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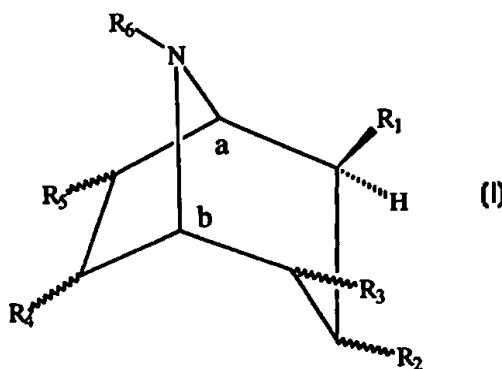
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(54) Title: TROPANE DERIVATIVES AND METHOD FOR THEIR SYNTHESIS

(57) Abstract

A compound of formula (I) wherein R₁ - R₆ have any of the values defined in the specification, as well as pharmaceutical compositions comprising a compound of formula (I), and methods for preparing and using compounds of formula (I) are described.



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TROPANE DERIVATIVES AND METHOD FOR THEIR SYNTHESIS

Background of the Invention

5 (R)-Cocaine or (-)-cocaine is a plant alkaloid purified from the leaves of *Erythroxylon coca* and has been a subject of scientific investigation since the late 1800s. It is one of the eight possible stereoisomeric forms of methyl 3-(benzoyloxy)-8-methyl-8-azabicyclo [3.2.1]octane-2 carboxylate. Cocaine has many physiological effects. It is a local anesthetic, and this property is
10 responsible for its early legitimate use in medicine. However, many newer compounds have been developed that are superior to cocaine for this purpose. Cocaine is also a powerful vasoconstrictant and, as such, has some current use in medicine during nasal or throat surgery where control of bleeding is desired. Cocaine also has very potent effects on the sympathetic nervous system, and it is
15 well known to increase heart rate and blood pressure.

In both animals and humans, cocaine is one of the most reinforcing drugs known, which has given rise to a serious cocaine abuse epidemic in the United States over the last 10-15 years (see e.g., Musto, *Sci. Amer.*, 256, 40 (1991)). From the point of view of drug abuse, the most relevant effects of the drug
20 include its ability to produce euphoria and its reinforcing effect. In addition to being a powerful reinforcer, cocaine also has properties common to other drugs subject to abuse. For example, tolerance occurs to some of its effects, and its psychological withdrawal syndrome takes place over a long time period, which includes periods of craving during which relapse to drug use often occur (see,
25 Gawin et al., *Arch. Gen. Psychiatry*, 43, 107 (1986)).

Over the past 10 years, there have been significant advances in understanding the mechanism of action of cocaine. The development of drug self-administration as a useful animal model for reinforcing properties has led to exploration of many of the physiological, neurochemical, neuroanatomical, and
30 pharmacological correlates (Griffiths, in *Advances in Substance Abuse*, Vol., 1, N.K. Mello, ed., UAI Press Inc., Greenwich Conn. (1980) at pages 1-90)).

Several studies have shown that cocaine binds to the dopamine transporter and inhibits dopamine transport (Kubar et al., *NIDA Research Monograph* (1988) at pages 14-22). In addition, drugs that are potent in

- maintaining self-administration, such as nomifensine, methylphenidate and mazindol, are also potent inhibitors of binding at the transport site for dopamine, whereas compounds that are weak in self-administration studies are correspondingly weak inhibitors of the binding site. For example, Ritz et al. (5 *Science*, 237 1249 (1987)) showed that the relative ability of several compounds to displace [³H]mazindol binding to the dopamine transporter from rat striatum was correlated to drug self-administration studies in nonhuman primates. Similarly, Berman et al. (*J. Pharmacol. Exp. Ther.*, 251, 150 (1989)) found a good correlation between displacement of [³H]-cocaine binding to the transporter (10 and drug self-administration behavior in squirrel monkeys. The most potent compounds in binding and behavioral studies reported from both investigations were 3β-phenyltropane-2β-carboxylic acid methyl ester and 3β-(p-fluorophenyl)tropane-2β-carboxylic acid methyl ester (Clark et al., *J. Med. Chem.*, 16, 1260 (1973)).
- 15 Only a limited number of cocaine analogs have been available to study the structural requirements for binding to the dopamine transporter and for cocaine-like reinforcing properties. For example, Carroll et al. (*J. Med. Chem.*, 34, 2719 (1991); *Eur. J. Pharm.*, 184, 329 (1990)) synthesized and measured the binding affinity of a number of new 3β-(p-substituted phenyl)tropane-2β- (20 carboxylic acid methyl esters and measured their ability to inhibit the binding of 0.5 nM [³H]-3β-(p-fluorophenyl)tropane-2β-carboxylic acid methyl ester to the dopamine transport site of rat striata. The iodo- and chloro- substituted derivatives were found to have a potency of approximately 80 times that of (-)-cocaine in this *in vitro* assay. Carroll et al. (*J. Med. Chem.*, 35, 969 (1992)) (25 proposed that specific hydrogen bond donor groups are present within the cocaine recognition site which bind to the 2-carbomethoxy group.

However, despite some success, a need exists for novel analogs of cocaine. Such compounds may exhibit enhanced analgesic and/or vasoconstrictive properties, or potentially be more selective than (-)-cocaine; or (30 such analogs may inhibit the uptake of dopamine or serotonin and, therefore, be useful for treating a disease or condition such as Parkinson's disease, depression, or obesity. Such compounds may also be useful for treating cocaine abuse. A

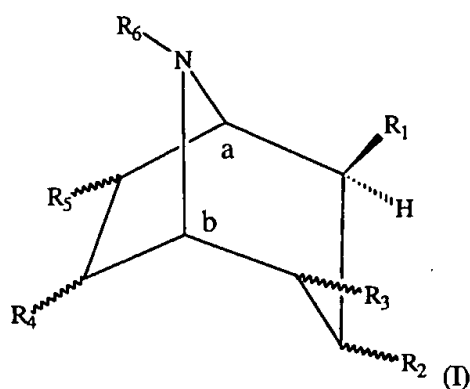
need also exists for additional methods to synthesize cocaine analogs

Additionally, a need exists for cocaine analogs which can be employed to further characterize the cocaine binding site(s), and to assist in the development of additional specific cocaine binding site agonists and antagonists.

5

Summary of the Invention

The present invention provides a compound of formula (I):



10 wherein

R_1 is hydrogen, aryl, aryl(C_1 - C_4)alkyl, (C_1 - C_4)alkyl, OR_7 , or $N(R_8)_2$;

R_2 is aryl or aryl(C_1 - C_4)alkyl;

R_3 is hydrogen, (C_1 - C_4)alkyl, (C_2 - C_4)alkenyl or (C_2 - C_4)alkynyl;

R_4 and R_5 are independently hydrogen, halo, CN, OR_9 , $COOR_{10}$,

15 aryl SO_2 -, or $-CH_2NHR_{11}$;

R_6 is hydrogen, (C_1 - C_4)alkyl, (C_1 - C_4)alkenyl, (C_1 - C_4)alkynyl, aryl, or aryl(C_1 - C_4)alkyl;

R_7 is hydrogen, (C_1 - C_4)alkyl, (C_1 - C_5)alkanoyl, arylcarbonyl or aryl (C_1 - C_5)alkanoyl;

20 each R_8 is independently hydrogen, (C_1 - C_4)alkyl, (C_1 - C_4)alkanoyl, aryl, aryl(C_1 - C_4)alkyl, or arylcarbonyl;

R_9 is hydrogen, (C_1 - C_4)alkyl, (C_1 - C_5)alkanoyl, or arylcarbonyl;

R_{10} is hydrogen or (C_1 - C_4)alkyl; and

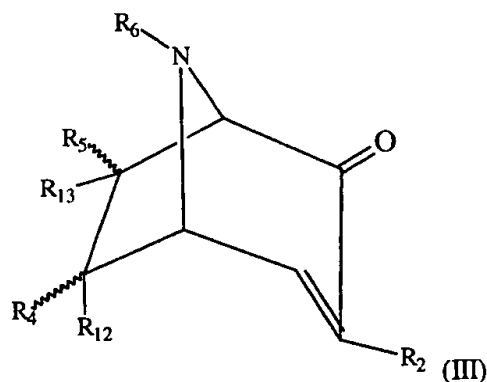
R_{11} is hydrogen or (C_1-C_4) alkyl;

wherein any aryl in R_1 , R_2 , and R_6-R_9 may optionally be substituted with 1, 2, or 3 substituents independently selected from the group consisting of halo (preferably I or Cl), CF_3 , (C_1-C_4) alkoxy, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, $(C_1-$

5 $C_4)$ alkynyl, amino, nitro cyano, and aryl;

or a pharmaceutically acceptable salt thereof.

The present invention also provides a method of synthesizing a compound of formula (III):



10

wherein

R_2 is aryl or aryl (C_1-C_4) alkyl;

R_4 and R_5 are independently hydrogen, halo, CN, OR_9 , $COOR_{10}$,

$-CH_2NHR_{11}$, or a chiral auxiliary;

15 R_6 is hydrogen, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, aryl, or aryl (C_1-C_4) alkyl;

R_9 is hydrogen, (C_1-C_4) alkyl, (C_1-C_5) alkanoyl, or arylcarbonyl;

R_{10} is hydrogen or (C_1-C_4) alkyl;

R_{11} is hydrogen or (C_1-C_4) alkyl; and

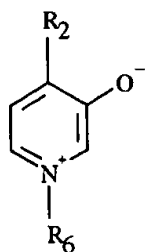
20 R_{12} and R_{13} are each hydrogen; or one of R_{12} and R_{13} is hydrogen, and the other is a chiral auxiliary (such as for example a (+)-(R)-p-tolylsulfinyl, or a (-)-(S)-p-tolylsulfinyl substituent).

wherein any aryl in R_2 , R_6 and R_9 may optionally be substituted with 1, 2,

5

or 3 substituents independently selected from the group consisting of halo (preferably I or Cl), CF_3 , $(\text{C}_1\text{-C}_4)\text{alkoxy}$, $(\text{C}_1\text{-C}_4)\text{alkyl}$, $(\text{C}_2\text{-C}_4)\text{alkenyl}$, $(\text{C}_2\text{-C}_4)\text{alkynyl}$, amino, nitro cyano, or aryl;
comprising reacting a compound of formula (IV):

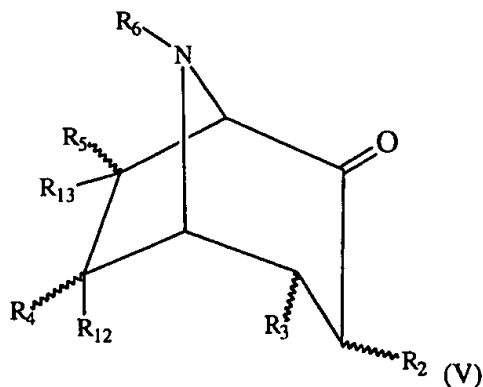
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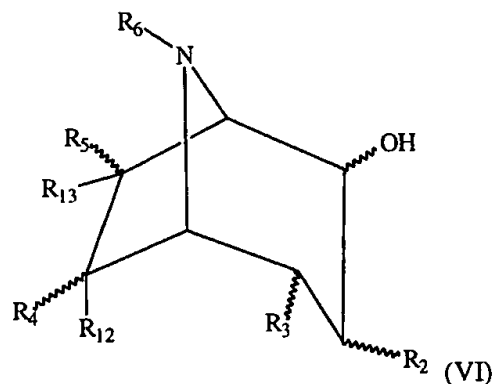
(IV)

with a compound of formula $\text{R}_4\text{CH}_2=\text{CHR}_5$. Preferably, the reaction is
10 conducted with heating in a suitable organic solvent, i.e., under reflux conditions.

The method of the invention may further comprise reacting the compound of formula (III) with $\text{R}_3\text{-MgBr}$, where R_3 is $(\text{C}_1\text{-C}_4)\text{alkyl}$, $(\text{C}_2\text{-C}_4)\text{alkenyl}$ or $(\text{C}_2\text{-C}_4)\text{alkynyl}$; a source of Cu(I) , and a hydroxy protecting reagent
15 such as $((\text{C}_1\text{-C}_4)\text{alkyl})_3\text{SiCl}$ followed by removal of the protecting group, to yield a compound of formula (V):



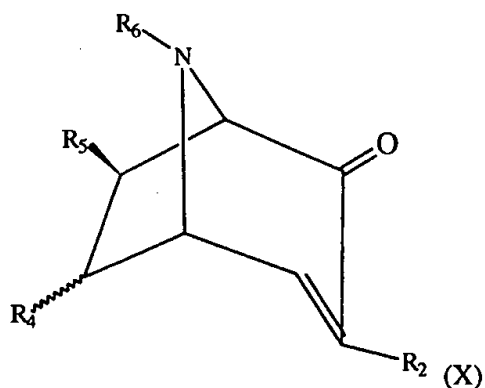
According to the invention, the method further comprises reducing the keto group in the compound of formula (V) to yield a compound of formula (VI):



- 5 and reacting the compound of formula (VI) with an anhydride of the formula $\text{CH}_3\text{C}(\text{O})\text{O}-\text{R}_7$, where R_7 is $(\text{C}_1-\text{C}_5)\text{alkanoyl}$, arylcarbonyl or $\text{aryl } (\text{C}_1-\text{C}_5)\text{alkanoyl}$ to yield a compound of formula (I): wherein R_1 is OR_7 .

- According to the invention, for a compound of formula (III, IV, or V) wherein one of R_{12} and R_{13} is hydrogen and the other is a chiral auxiliary, the
 10 method may further comprise removing the chiral auxiliary to give a corresponding compound of formula (III, IV, or V) wherein R_{12} and R_{13} are each hydrogen.

The invention further provides a method of synthesizing a compound of formula (X):



wherein

R_2 is aryl or aryl(C₁-C₄)alkyl;

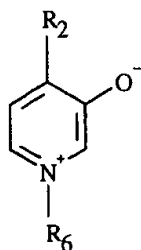
R_4 and R_5 are hydrogen or arylSO₂-, provided that one of R_4 or R_5 is H and the other is arylSO₂-; and

5 R_6 is hydrogen, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, aryl, or aryl(C₁-C₄)alkyl;

wherein any aryl in R_2 or R_6 may optionally be substituted with 1, 2, or 3 substituents independently selected from the group consisting of halo (preferably I or Cl), CF₃, (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₂-C₄)alkenyl, (C₂-C₄)alkynyl, amino,

10 nitro cyano, and aryl;

comprising reacting a compound of formula (IV):



(IV)

with CH₂=CH-SO₂aryl.

15

Brief Description of the Drawings

Figure 1 illustrates the synthesis of intermediates useful for preparing compounds of formula (I).

Figure 2 illustrates the synthesis of certain compounds of formula (I).

20 Figure 3 illustrates an alternative method of synthesizing compounds of formula (I).

Figure 4 illustrates the synthesis of certain compounds of formula (I) as prepared in Examples 8-11.

25 Figure 5 illustrates the synthesis of certain compounds of formula (I) as prepared in Examples 12-14.

Figure 6 illustrates the synthesis of certain compounds of formula (I) as prepared in Examples 15-21.

Figure 7 illustrates the synthesis of certain compounds of formula (I) as prepared in Examples 5-6.

5 Figure 8 shows biological data for representative compounds of formula (I).

Detailed Description

The following definitions are used, unless otherwise described:

halo is fluoro, chloro, bromo, or iodo. Alkyl, alkoxy, alkenyl, alkynyl, etc.

10 denote both straight and branched groups; but reference to an individual radical such as "propyl" embraces only the straight chain radical, a branched chain isomer such as "isopropyl" being specifically referred to. Aryl denotes a phenyl radical or an ortho-fused bicyclic carbocyclic radical having about nine to ten ring atoms in which at least one ring is aromatic.

15 It will be appreciated by those skilled in the art that compounds of the invention having one or more chiral centers may exist in and be isolated in optically active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic, or stereoisomeric form, or mixtures
20 thereof, of a compound of the invention, which possess the useful properties described herein. Preferably, the compound of formula (I) comprises the enantiomeric 8-azabicyclo[3.2.1] ring system corresponding to the 8-azabicyclo[3.2.1] ring system of (R)-cocaine or (-)-cocaine, wherein for a compound of formula (I), the carbon designated "a" has the (R) configuration
25 and the carbon designated "b" has the (S) configuration. In formula (I), R_1 is in the β -position, as indicated by the wedged bond.

Specific and preferred values listed below for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

30 Specifically, (C_1-C_4) alkyl can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, or sec-butyl; (C_1-C_4) alkoxy can be methoxy, ethoxy, propoxy, isopropoxy, butoxy, iso-butoxy, or sec-butoxy; (C_2-C_4) alkenyl can be vinyl, allyl,

1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, or 3-butenyl; (C₂-C₄)alkynyl can be ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, or 3-butyne; (C₁-C₅)alkanoyl can be acetyl, propanoyl, butanoyl, or pentanoyl; and aryl can be phenyl, indenyl, or naphthyl; aryl(C₁-C₄)alkyl can be benzyl or phenethyl; and arylcarbonyl can be benzoyl.

Specifically: R₁ can be hydrogen, OR₇, or N(R₈)₂; or R₁ can be OR₇, or N(R₈)₂; R₃ can be (C₁-C₄)alkyl, (C₂-C₄)alkenyl or (C₂-C₄)alkynyl; or R₃ can be (C₂-C₄)alkenyl or (C₂-C₄)alkynyl; and R₇ can be (C₁-C₅)alkanoyl, arylcarbonyl, or aryl (C₁-C₅)alkanoyl; .

10 A specific group of compounds are compounds of formula (I) wherein R₁ is hydrogen, aryl, (C₁-C₄)alkyl, OR₇, or N(R₈)₂; wherein any aryl in R₁ may optionally be substituted with 1, 2, or 3 substituents independently selected from the group consisting of halo (preferably I or Cl), CF₃, (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₄)alkenyl, (C₁-C₄)alkynyl, amino, nitro and cyano; or a
15 pharmaceutically acceptable salt thereof.

Another specific group of compounds are compounds of formula (I) wherein R₁ is aryl, aryl(C₁-C₄)alkyl, OR₇, or N(R₈)₂; or a pharmaceutically acceptable salt thereof.

Another specific group of compounds are compounds of formula (I)
20 wherein R₂ is aryl or aryl(C₁-C₄)alkyl; wherein the aryl is substituted with 1, 2, or 3 substituents independently selected from the group consisting of halo (preferably I or Cl), CF₃, (C₁-C₄)alkoxy, (C₁-C₄)alkenyl, (C₁-C₄)alkynyl, amino, nitro and cyano; or a pharmaceutically acceptable salt thereof.

Another specific group of compounds are compounds of formula (I)
25 wherein one of R₄ and R₅ is hydrogen, and the other is halo, CN, OR₉, COOR₁₀, arylSO₂-, or -CH₂NHR₁₁; or a pharmaceutically acceptable salt thereof.

A preferred compounds is compound 49, or compound 37; or a pharmaceutically acceptable salt thereof.

The present invention provides a method of synthesizing tropane analogs
30 which makes it possible to prepare structures containing variable substituents at positions 2, 3, 4, 6 and 7 of the tropane skeleton. The present method can be used to synthesize structures previously found useful to exhibit useful activity in

the treatment of Parkinson's disease. In addition, the present method may be used to synthesize novel tropane analogs. Efficient access to diverse cocaine analogs may also provide additional therapeutic agents, as well as providing means to manipulate the structure of cocaine to derive partial agonists for use in the discovery of anti-abuse therapies.

Tropane analogs of formula (I) can be synthesized as shown in Figures 1-7. The number following the named compounds refer to the numbered compounds. A pyridinium betaine-based dipolar cycloaddition route was used to obtain the troponone of formula III, and this intermediate was transformed to products of formula I. Oxidopyridinium betaine was obtained as a crystalline, storable reagent, starting from the known 4-phenyl-3-hydroxypyridine **1** (Figure 1)(Commins et al., *J. Heterocyclic Chem.* 22:1419 (1985)). Pyridine **1** was treated with methyl iodide, and the resulting hydroxypyridinium salt **2** was stirred with the ion exchange resin IRA 400 (OH) in methanol to afford the desired betaine **3**.

The betaine **3** was investigated for its ability to undergo dipolar cycloaddition chemistry with 2π addends. Using acrylonitrile as the test addend it was found that the 1,3-dipolar cycloaddition reaction proceeded readily when carried out at reflux temperatures for 3 hours. Two major adducts **4a** and **4b** were isolated. These compounds are of a single regiochemistry and of either 6β (**4a**, 38% isolated yield) or 6α (**4b**, 43%) stereochemistry. In addition, small amounts of the other two regioisomeric products were isolated (**4c**, 7β -isomer, 5% and **4d**, 7α isomer, 17%, see Figure 1 and Table 1). Similar results were achieved upon using phenyl vinylsulfone as the dipolarophile and acetonitrile as solvent. After 3 hours at reflux, the resulting mixture contained **5a** as the major reaction product together with small amounts of the isomers **5b** and **5c**. In this particular case isomer **5d** could not be detected (Table 1). The results achieved using methyl acrylate are also provided in the accompanying Table. NMR assignments of all of the pure isomers were made through the use of COSY, DEPT, and HETCOR experiments.

Table 1. Products and isolated yields obtained for the reaction of betaine **3** with

three representative dipolarophiles.

Compound Number*	X	Y	W	Z	Yield (%)
4a	CN	H	H	H	38
4b	H	CN	H	H	43
4c	H	H	CN	H	5
4d	H	H	H	CN	17
5a	SO ₂ Ph	H	H	H	60
5b	H	SO ₂ Ph	H	H	16
5c	H	H	SO ₂ Ph	H	15
5d	H	H	H	SO ₂ Ph	0
6a	CO ₂ Et	H	H	H	33
6b	H	CO ₂ Et	H	H	20
6c	H	H	CO ₂ Et	H	26
6d	H	H	H	CO ₂ Et	12

*See Figure 1 for structures of compound 4-6.

To investigate the general utility of these tropenone intermediates to afford access to a wide variety of 3-phenyltropanes, further chemistry was carried out on **4a**. For example, reaction of **4a** with *n*-butylmagnesium bromide in the presence of cuprous bromide and trimethylsilyl chloride (Horiguchi et al., *Tetrahedron Lett.* 27(34):4025 (1986)) at -78 °C furnished the conjugate addition product **7a** in 98% yield (Figure 2). The ketone **7a** was reduced in turn with sodium borohydride to afford predominantly the 2 α alcohol **8a** in 83% yield. Next, the alcohol was treated with phenyl thionochloroformate and *n*-BuLi in THF (Berkowitz et al., *J. Org. Chem.*, 61:4666 (1996)) at -78 °C to provide the thionocarbonate which was deoxygenated with Bu₃SnH to the tropane **9a**. Alternatively, the alcohol **8a** is dehydrated with the Burgess reagent (Burgess et al., *J. Org. Chem.*, 38:26 (1973)) to provide the olefin **10a**. Subsequent hydrogenation provided a readily separable 6:4 mixture of **9a** and **13a**.

While the sequence of reactions shown in Figure 2 provides ready access to a new series of tropane derivatives possessing substitution at the 6 and/or 7-positions, together with the α -stereochemistry of the phenyl substituent and consequently a boat conformation for the piperidine ring, efficient access was

desired to those analogues possessing cocaine-like stereochemistry. Specifically, an alternate method was developed to transform the troponone intermediate to the tropane having a chair-like conformation for its piperidine ring and with the substituents at positions 2 and 3 having β stereochemistry.

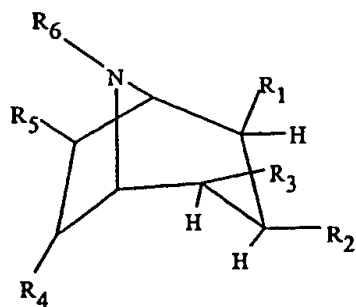
5 As shown in Figure 3, the tropane derivatives of formula I may be obtained starting from the intermediate VI via the reduction of the ketone 4a to alcohol 11a using sodium borohydride/cerium chloride in methanol (Luche, *J. Am. Chem. Soc.*, 100:2226 (1978)). This alcohol was converted to its allylic acetate 12a with acetic anhydride and pyridine, and a cuprous cyanide catalyzed
10 anti S_N2' reaction (Tseng et al., *J. Org. Chem.* 51:2884 (1986)) was carried out using *n*-butylmagnesium bromide as nucleophile to afford the olefin 10a. This olefin was subjected in turn to hydrogenation (30 psi, MeOH) over palladium on carbon to yield the 2 β ,3 β -isomer 13a together with the product 9a derived from β -face hydrogenation. This S_N2' chemistry thus affords a higher yielding route
15 to compound 13a than the dehydration method shown in Figure 2.

The foregoing chemistry is expected to be applicable to a range of other tropenones derived from any of a number of other reactive dipolarophiles. The dipolar cycloaddition strategy can be used to create a stereodefined library of tropane structures for biological assay. The invention also provides the use of
20 dipolarophiles bearing chiral auxiliary groups to permit access to optically pure tropanes as well as the attachment of the betaine to resin supports for use in combinatorial chemistry approaches.

A specific compound of formula I is a compound of formula XI:

25

30



(XI)

wherein

R_1 is H, OR_7 where R_7 is H, $(C_1-C_4)alkyl$, $(C_1-C_4)alkylC(O)-$, $(C_5-C_7)arylC(O)-$; NHR_8 where R_8 is H, $(C_1-C_4)alkyl$, $(C_1-C_4)alkylC(O)-$ or $(C_5-C_7)arylC(O)-$;

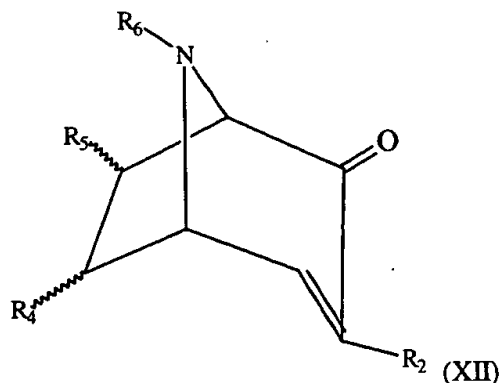
- 5 R_2 is phenyl or benzyl (preferably phenyl), each optionally substituted with halo (preferably I or Cl), CF_3 , $(C_1-C_4)alkoxy$, $(C_1-C_4)alkyl$, $(C_1-C_4)alkenyl$, $(C_1-C_4)alkynyl$, amino, nitro or $(C_5-C_7)aryl$;

R_3 is $(C_1-C_4)alkyl$, $(C_1-C_4)alkenyl$ or $(C_1-C_4)alkynyl$;

- R_4 and R_5 are independently H, halo, CN, OR_9 where R_9 is H, $(C_1-C_4)alkyl$, $(C_1-C_4)alkylC(O)-$, $(C_5-C_7)arylC(O)-$; $COOR_{10}$ where R_{10} is H or $(C_1-C_4)alkyl$; or CH_2NHR_{11} where R_{11} is H or $(C_1-C_4)alkyl$; and

R_6 is H, $(C_1-C_4)alkyl$, $(C_1-C_4)alkenyl$, $(C_1-C_4)alkynyl$ or benzyl (preferably $(C_1-C_4)alkyl$); or a stereoisomer thereof; or a pharmaceutically acceptable salt thereof.

- 15 One specific embodiment of the invention provides a method of synthesizing a compound of formula (XII):



wherein

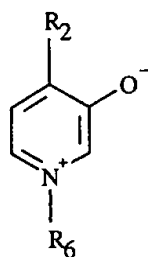
R_2 is phenyl or benzyl, optionally substituted with halo, CF_3 , $(C_1-C_4)alkoxy$, $(C_1-C_4)alkyl$, $(C_1-C_4)alkenyl$, $(C_1-C_4)alkynyl$, amino, nitro or $(C_5-C_7)aryl$;

- 20 R_4 and R_5 are independently H, halo, CN, OR_9 where R_9 is H, $(C_1-C_4)alkyl$, $(C_1-C_4)alkylC(O)-$, $(C_5-C_7)arylC(O)-$; $COOR_{10}$ where R_{10} is H or $(C_1-C_4)alkyl$; or CH_2NHR_{11} where R_{11} is H or $(C_1-C_4)alkyl$, provided that one of R_4

and R_5 is H; and

R_6 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl or benzyl;
comprising the step of reacting a compound of formula (IV):

5



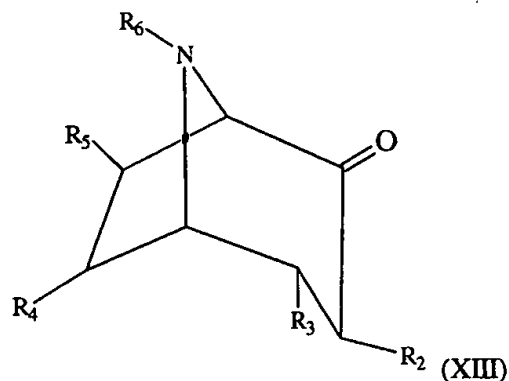
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(IV)

with $CH_2=CH-R$, where R is halo, CN, OR_9 , $COOR_{10}$, or CH_2NHR_{11} . Preferably, the reaction can be conducted with heating in a suitable organic solvent, i.e., under reflux conditions.

15

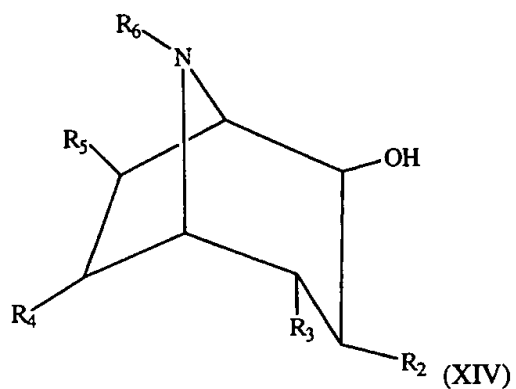
According to the invention, this specific embodiment may further comprise the step of reacting the compound of formula (XII) with R_3-MgBr , where R_3 is (C_1-C_4) alkyl, (C_1-C_4) alkenyl or (C_1-C_4) alkynyl; a source of Cu(I), and a hydroxy protecting reagent such as $((C_1-C_4)alkyl)_3SiCl$ followed by removal of the protecting group, to yield a compound of formula (XIII):



20

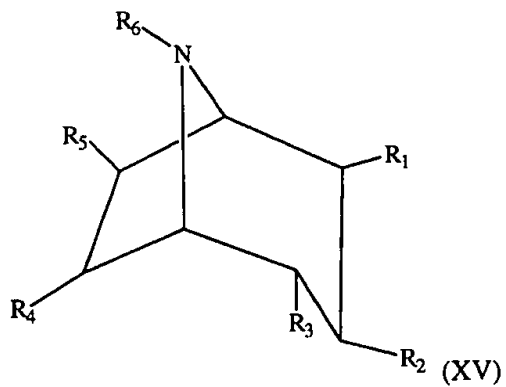
According to the invention, this specific embodiment may further comprises the steps of reducing the keto group in the compound of formula (XIII) to yield a compound of formula (XIV):

15



and reacting the compound of formula (XIV) with an anhydride of the formula $CH_3C(O)O-R_7$, where R_7 is $(C_1-C_4)alkylC(O)-$ or $(C_5-C_7)arylC(O)-$ to yield a compound of formula (XV):

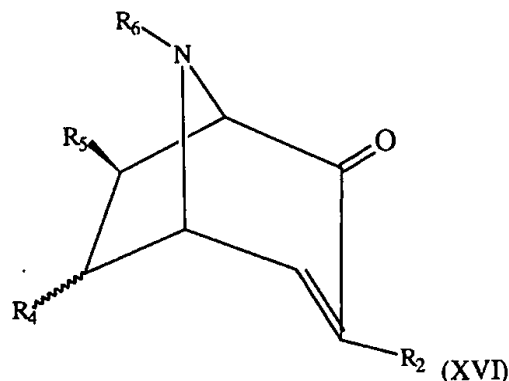
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10 where R_1 is OR_7 .

In another specific embodiment the invention provides a method of synthesizing a compound of formula (XVI):

16



wherein

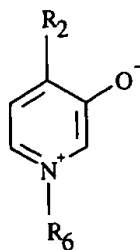
R₂ is phenyl or benzyl, optionally substituted with halo, CF₃, (C₁-C₄)alkoxy, (C₁-C₄)alkyl, (C₁-C₄)alkenyl, (C₁-C₄)alkynyl, amino, nitro or (C₅-

5 C₇)aryl;

R₄ and R₅ are H or SO₂Ph, provided that one of R₄ or R₅ is H and the other is SO₂Ph; and

R₆ is H, (C₁-C₄)alkyl, (C₁-C₄)alkenyl, (C₁-C₄)alkynyl or benzyl;

comprising the steps of reacting a compound of formula (IV):



(IV)

10

with CH₂=CH-SO₂Ph.

In cases where compounds are sufficiently basic or acidic to form stable nontoxic acid or base salts, administration of the compounds as salts may be appropriate. Examples of pharmaceutically acceptable salts are organic acid

15 addition salts formed with acids which form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, α-ketoglutarate, and α-glycerophosphate.

Suitable acid addition salts of inorganic acids may also be formed, including hydrochloride, sulfate, nitrate, bicarbonate, and carbonate salts.

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example calcium) salts of carboxylic acids can also be made.

The compounds of formula I can be formulated as pharmaceutical compositions and administered to a mammalian host, such as a human patient in a variety of forms adapted to the chosen route of administration, i.e., orally or parenterally, by intravenous, intramuscular, topical or subcutaneous routes.

Thus, the present compounds may be systemically administered, e.g., orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.

The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in

addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

The active compound may also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the active compound or its salts can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form must be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for

example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the
5 active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus
10 any additional desired ingredient present in the previously sterile-filtered solutions.

For topical administration, the present compounds may be applied in pure form, i.e., when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination
15 with a dermatologically acceptable carrier, which may be a solid or a liquid.

Useful dosages of the compounds of formula I can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949.

20 Generally, the concentration of the compound(s) of formula I in a liquid composition, such as a lotion, will be from about 0.1-25 wt-%, preferably from about 0.5-10 wt-%. The concentration in a semi-solid or solid composition such as a gel or a powder will be about 0.1-5 wt-%, preferably about 0.5-2.5 wt-%. Single dosages for injection, infusion or ingestion will generally vary
25 between 50-1500 mg, and may be administered, i.e., 1-3 times daily, to yield levels of about 0.5 - 50 mg/kg, for adults.

Accordingly, the invention includes a pharmaceutical composition comprising a compound of formula I as described hereinabove; or a pharmaceutically acceptable salt thereof; in combination with a pharmaceutically
30 acceptable carrier.

The ability of representative compounds of the invention to displace [³H]mazindol was determined using Test A below. [³H]Mazindol has been

shown to label the cocaine binding sites on the dopamine transporter of rat striatal membranes (Kozikowski et al. *Med. Chem. Res.*, **1991**, 312-321), and it binds with high affinity to a single, sodium-dependent site in striatal membranes representing the dopamine carrier. Additionally, the ability of representative compounds of the invention to inhibit high-affinity uptake of [³H]dopamine and [3H]serotonin into striatal nerve endings (synaptosomes) was determined using known protocols (see M.C. Ritz et al. *Science*, **1988**, 1219; and by M.J. Kuhar et al. *Life Sci.*, **1973**, 13, 1623-1634), as described in Test B below. Results from Test A and Test B are presented in Figure 8.

10 Test A

[³H]Mazindol binding assay: Caudate nuclei were homogenized in buffer consisting of 5 mM HEPES, 5mM KCl and 100 mM NaCl (pH 7.4) and centrifuged for 10 min at 39,000 x g. The pellet was resuspended in buffer and centrifuged again. Finally, the pellet was resuspended in 30 volumes of buffer, pelleted at 15,000 x g and frozen at -80°C until used. The striatal homogenates were thawed by resuspension in the buffer described above at 75-125 µg protein/ml and incubated with [³H]mazindol, with or without competing drugs, for 60 min in a 4 °C cold room. Non-specific binding was determined with 30 µM cocaine. The bound and free [³H]mazindol was separated by rapid vacuum filtration over Whatman GF/C filters, using a Brandel M24R cell harvester, followed by two washes with 5 ml of cold buffer. Radioactivity on the filters was then extracted by vortexing with 5 ml of scintillant and the vials counted. IC₅₀ values were determined using the computer program LIGAND.

Test B

25 Uptake of [³H]dopamine and [³H]serotonin was carried out using synaptosomes from the same brain regions as described above for binding assays. A Krebs phosphate buffer, pH 7.4, containing 1µM pargyline, dextrose (1.9 mg/ml), and ascorbic acid (0.2 mg/ml) was used. Synaptosomes were prepared by homogenizing fresh tissue in 20 volumes of ice-cold 0.32 M sucrose using a glass-teflon homogenizer. Nuclei and large tissue fragments were removed by centrifugation at 800 x g for 10 minutes. The supernatant was centrifuged at 20,000 x g for 15 minutes to collect synaptosomes in a pellet. The

pellet was resuspended in 0.32 M sucrose at a concentration of 15, 100 or 10 mg/ml original wet weight, and diluted 10 fold in the assay tubes. The final assay volume was 1.0 ml and the duration of incubation at 30 °C was 3 minutes so that uptake was linear with time in contrast to binding assays where binding
5 had reached equilibrium.

K_i values were determined using serial dilutions of the analogues. A thirty minute preincubation of the analogues with the tissue was utilized before uptake was initiated by adding tritiated substrate. The preincubation was utilized to allow analogue and transporters to reach an equilibrium so that kinetic effects
10 were not a significant factor. K_i values were determined using standard techniques.

Generally, compounds of the invention can bind to the cocaine recognition sight. Thus, the present compounds may be useful to treat drug addiction and in particular, cocaine addiction. Accordingly, the invention
15 includes a method for the treatment of drug addiction in a human comprising administering to a human in need of such treatment a pharmaceutically effective dose of at least one compound of formula I; or a pharmaceutically acceptable salt thereof. Additionally, the invention provides a therapeutic method comprising inducing analgesia or vasoconstriction in a mammal, such as a
20 human, by administering an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof.

Compounds of the invention have also been shown to inhibit dopamine and/or serotonin uptake, and may be useful to treat diseases or conditions wherein the modulation of dopamine or serotonin uptake is desirable.
25 Accordingly, the invention includes a method for treating a disease or condition in a human, in which the activity of dopamine or serotonin has been implicated and modulation of dopamine or serotonin uptake is desired comprising administering to a human in need of such treatment, a pharmaceutically effective dose of at least one compound of formula I; or a pharmaceutically acceptable salt
30 thereof. The present compounds may be particularly useful to treat depression, obesity or Parkinson's disease.

Compounds of the invention may also be useful as imaging agents when

labeled with a radionuclide. The radionuclide (such as tritium, iodine-125, iodine-131, iodine-123, astatine-210, carbon-11, carbon-14, nitrogen-13, fluorine-18) may be incorporated into, or attached directly to the core structure, as by halogenation; or the radionuclide (such as Tc-99m, Re-186) may be attached to a linking group or bound by a chelating group which is then attached to the compound of formula I directly, or by means of a linker. Radiolabeling techniques such as these are routinely used in radiopharmaceutical chemistry (see for example J.L. Nuemeyer et al. *J. Med. Chem.* **1994**, 37, 1558-1561 and J.L. Nuemeyer et al. *J. Med. Chem.* **1996**, 39, 543-548). Accordingly, the invention also provides a radiolabeled compound comprising a radionuclide bound to a compound of formula I; or a pharmaceutically acceptable salt thereof, as well as a method of using such a radiolabeled compound as an imaging agent.

The 2 β ,3 α diaryl derivatives, compounds **49** and **37**, are highly selective for the dopamine transporter relative to the serotonin transporter. Due to this selectivity, radiolabeled compound comprising compound **49** or **37** may be particularly useful as imaging agents.

The invention also provides a method of imaging the brain of a mammal (i.e. a human) comprising administering to said mammal, a detectable amount of a radiolabeled compound, comprising radionuclide bound to a compound of formula (I), or a pharmaceutically acceptable salt thereof; and subsequently detecting the presence of said radiolabeled compound.

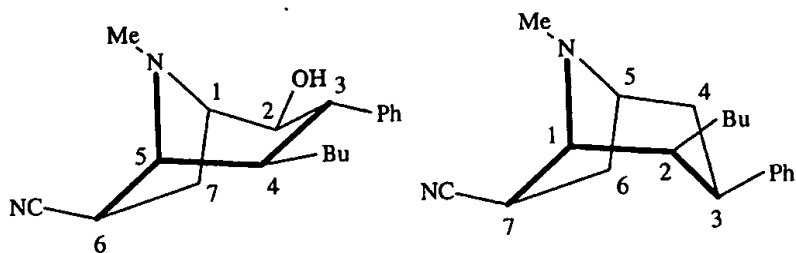
The invention also provides a compound of formula I for use in medical therapy (preferably for use in inducing analgesia or vasoconstriction in a mammal, or for use in treating cocaine abuse, depression, obesity, or Parkinson's disease), as well as the use of a compound of formula I for the manufacture of a medicament for inducing analgesia or vasoconstriction in a mammal, or for treating cocaine abuse, depression, obesity, or Parkinson's disease in a mammal, such as a human.

The invention also provides a radiolabeled compound comprising a radionuclide bound to a compound of formula I for use in medical imaging, as well as the use of a radiolabeled compound comprising a radionuclide bound to a compound of formula I, for the manufacture of a medicament useful for medical

imaging.

The invention will be further described by reference to the following non-limiting examples wherein, unless otherwise noted:

- a. Starting materials were obtained from Aldrich Chemicals or from other commercial suppliers;
- b. Diethyl ether was purified by distillation from phosphorous pentoxide;
- c. THF was freshly distilled under nitrogen from sodium-benzophenone;
- d. IR spectra was recorded on an ATI Mattson spectrophotometer;
- e. ^1H and NMR spectra were obtained with a Varian Unity Inova at 300 and 75.46 MHz respectively. ^1H chemical shifts (δ) are reported in ppm downfield from internal TMS;
- f. ^{13}C chemical shifts are referred to: CDCl_3 (central peak, $\delta = 77.0$ ppm), benzene- d_6 (central peak, $\delta = 128.0$ ppm) or $\text{DMSO}-d_6$ (central peak, $\delta = 39.7$ ppm);
- g. NMR assignments were made with COSY, DEPT and HETCOR programs;
- h. The subscript numbers are used to identify the protons in the tropane rings according to the following numbering scheme:



- i. Melting points were determined in Pyrex capillaries with a Thomas Hoover Unimelt apparatus and are uncorrect;
- j. MS were measured in the EI mode with an ionization potential of 70 eV;

- k. TLC were performed on Merck glass silica gel plates;
 l. column chromatography was performed using Merck silica gel 60 (60-200 mesh); and
 m. The following abbreviations are used: DMSO as dimethyl sulfoxide, ether as diethyl ether; THF as tetrahydrofuran; EtOAc as ethyl acetate; DCM as dichloromethane; MeOH as methanol; EtOH as ethanol; CDCl_3 as chloroform- d_1 .

Examples

10 Example 1. 4 β -Butyl-2-hydroxy-8-methyl-3 α -phenyl-8-azabicyclo[3.2.1]octane -6-exo-carbonitrile (8a).

To a solution of **7a** (0.55 g, 1.86 mmol) in EtOH (20 mL) was added portionwise NaBH_4 (0.21 g, 5.57 mmol). The resulting solution was stirred at 25 °C for 1 h then concentrated and the residue diluted with water (60 mL) and
 15 extracted with EtOAc (2 x 50 mL). The collected organic phase was washed with brine (80 mL), dried and concentrated under reduced pressure. The crude mixture containing the two hydroxy isomers was purified by flash chromatography on silica gel using EtOAc/*n*-hexane as eluant. 2 α -hydroxy derivative (0.45 g, 81%): white solid; R_f = 0.8 (EtOAc/*n*-hexane 1/1); ^1H NMR (benzene- d_6) δ 0.633 (d, OH, $J_{\text{OH-2}}$ = 3.0 Hz), 0.721 (t, 3 H, J = 6.9 Hz), 0.9-1.15 (m, 5 H), 1.16-1.30 (m, 1 H), 1.358 (dt, H_4 , $J_{4,3}$ = 11.1 Hz, $J_{4,1'}$ = $J_{4,1''}$ = 6.0 Hz), 1.837 (dt, $\text{H}_{7\text{ex}}$, $J_{7\text{ex-1}}$ = $J_{7\text{ex-6}}$ = 6.5 Hz, $J_{7\text{ex-7en}}$ = 11.1 Hz), 2.270 (s, 3 H), 2.373 (dd, H_6 , $J_{6,7\text{en}}$ = 9.0 Hz, $J_{6,7\text{ex}}$ = 7.1 Hz), 2.693 (dd, $\text{H}_{7\text{en}}$, $J_{7\text{en-7ex}}$ = 12.9 Hz, $J_{7\text{en-6}}$ = 9.6 Hz), 2.744 (dd, H_3 , $J_{3,2}$ = 4.5 Hz, $J_{3,4}$ = 11.4 Hz), 3.105 (dd, H_1 , $J_{1,2}$ = 8.4 Hz, $J_{1,7\text{ex}}$ = 6.9 Hz), 3.286 (s, H_5), 3.695 (qd, H_2 , $J_{2-\text{OH}}$ = 3.0 Hz, $J_{2,1}$ = 8.6 Hz, $J_{2,3}$ = 4.8 Hz), 6.85-6.98 (m, 2 H), 7.0-7.1 (m, 3 H); ^{13}C NMR (benzene- d_6) δ 14.10, 22.99, 26.73, 28.89, 34.40, 34.56, 42.03, 45.47, 47.19, 66.08, 70.57, 71.91, 123.95, 127.00, 128.89, 129.80, 140.40; Ms, m/z (%): 298 (M^+ , 16), 255 (34), 245 (10), 177 (39), 135 (30), 107 (71), 42 (100); IR (film) 3466, 2932,
 25 2231, 1451 cm^{-1} . 2 β -hydroxy derivative (0.05 g, 9%): colorless oil; R_f = 0.6 (EtOAc/*n*-hexane 1/1); ^1H NMR (CDCl_3) δ 0.74 (t, 3 H, J = 7.2 Hz), 0.7-0.95 (m, 1 H), 1.0-1.35 (m, 4 H), 1.37-1.7 (m, 3 H), 2.38 (dd, $\text{H}_{7\text{endo}}$, $J_{7\text{en-6}}$ = 6.0 Hz,

$J_{7en-7ex} = 12.6$ Hz), 2.44-2.60 (m, H_3 and H_{7exo}), 2.59 (s, 3 H), 2.89 (dd, H_6 , $J_{6-7en} = 6.0$ Hz, $J_{6-7ex} = 9.6$ Hz), 3.46 (bt, H_1 , $J = 4.8$ Hz), 3.63 (s, H_5), 4.27 (dd, H_2 , $J = 3.0$ Hz, $J = 10.5$), 7.1-7.4 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 13.93, 22.53, 27.57, 27.86, 29.75, 30.49, 42.56, 46.45, 46.67, 67.78, 68.65, 70.82, 124.03, 127.02, 128.61, 128.82, 138.12; Ms, m/z (%): 298 (M^+ , 14), 255 (43), 245 (4), 241 (52), 177 (12), 135 (27), 107 (24), 42 (100);

The intermediate **7a** was prepared as follows.

- a. **1-Methyl-4-phenyl-3-hydroxypyridinium iodide (2).** To a solution of **1** (4.1 g, 24.0 mmol) in acetone (100 mL) was added iodomethane (3.0 mL, 48.0 mmol). The mixture was refluxed for 3 h and stirred at 25 °C for 40 h then ether (100 mL) was added and the precipitated filtered off and washed with ether to afford compound **2** (6.8 g, 90%) as a pale yellow solid: mp 175 °C; 1H NMR ($DMSO-d_6$) δ 4.31 (s, 3 H), 7.53-7.61 (m, 3 H), 7.76-7.84 (m, 2 H), 8.07 (d, 1 H, $J = 6.0$ Hz), 8.35 (s, 1 H), 8.528 (d, 1 H, $J = 6.0$ Hz), 12.1 (bs, 1 H); ^{13}C NMR ($DMSO-d_6$) δ 47.46, 127.40, 128.81, 129.42, 130.20, 133.34, 133.55, 135.24, 142.27, 155.00.
- b. **1-Methyl-4-phenyl-3-hydroxypyridine (3).** A mixture of **2** (4.03 g, 12.9 mmol) and IRA-OH (400) resin (20 mL) in MeOH was stirred at 25 °C for 1 h then the basic resin was filtered off and washed several time with MeOH. The resulting clear solution was concentrated under reduced pressure to afford the compound **3** (2.21 g, 92%) as a pale yellow solid used in the next step without further purification: mp 154-157 °C; 1H NMR ($DMSO-d_6$) δ 3.97 (s, 3 H), 7.3-7.52 (m, 5 H), 7.38 (d, 1 H, $J = 7.5$ Hz), 8.04 (d, 1 H, $J = 8.1$ Hz), 8.053 (s, 1 H).
- c. **8-Methyl-2-oxo-3-phenyl-8-azabicyclo[3.2.1]oct-3-ene-6-carbonitrile and 8-methyl-2-oxo-3-phenyl-8-azabicyclo[3.2.1]oct-3-ene-7-carbonitrile (4a-d).** To a solution of **3** (2.21 g, 11.9 mmol) in acrylonitrile (20 mL) was added a small amount of hydroquinone and the mixture refluxed under nitrogen for 1 h then concentrated under reduced pressure. The four isomers **4a-d** present in the crude mixture were separated by flash chromatography on silica gel using EtOAc/*n*-hexane as eluant. **4a** (1.07 g, 37%): pale yellow solid; mp 129-130 °C; $R_f = 0.6$ (EtOAc/*n*-hexane 4/6); 1H NMR ($CDCl_3$) δ 2.19 (dd, H_{7endo} , $J_{7en-7ex} =$

- 12.8 Hz, $J_{7en-6} = 9.3$ Hz), 2.617 (s, 3 H), 2.78 (qd, H_{7exo} , $J_{7ex-6} = 3.3$ Hz, $J_{7ex-1} = 7.5$ Hz, $J_{7ex-7en} = 13.8$ Hz), 3.064 (dd, H_6 , $J_{6-7ex} = 3.6$ Hz, $J_{6-7en} = 9.0$ Hz), 3.837 (d, H_1 , $J_{1-7ex} = 7.5$ Hz), 4.183 (d, H_5 , $J_{5-4} = 5.4$ Hz), 6.967 (d, H_4 , $J_{4-5} = 5.4$ Hz), 7.36 (bs, 5 H); ^{13}C NMR ($CDCl_3$) δ 30.37, 31.63, 36.03, 64.72, 70.16, 121.34, 128.15, 128.29, 128.69, 133.08, 138.771, 141.12, 196.40. **4b** (1.23 g, 42%): pale yellow solid; mp 110-112 °C; $R_f = 0.42$ (EtOAc/*n*-hexane 8/2); 1H NMR ($CDCl_3$) δ 2.00 (dd, H_{7endo} , $J_{7en-7ex} = 13.8$ Hz, $J_{7en-6} = 5.7$ Hz), 2.476 (s, 3 H), 2.88 (qd, H_{7exo} , $J_{7ex-6} = 10.2$ Hz, $J_{7ex-7en} = 13.8$ Hz, $J_{7ex-1} = 7.8$ Hz), 3.446 (dt, H_6 , $J_{6-5} = J_{6-7en} = 5.4$ Hz, $J_{6-7ex} = 11.4$ Hz), 3.75 (d, H_1 , $J_{1-7ex} = 7.5$ Hz), 4.184 (t, H_5 , $J_{5-4} = J_{5-6} = 5.4$ Hz), 7.141 (d, H_4 , $J_{4-5} = 5.4$ Hz), 7.3-7.5 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 29.93, 30.72, 36.83, 62.45, 70.67, 119.623, 128.26, 128.46, 128.66, 133.33, 139.84, 142.08, 195.99. **4c** (0.15 g, 5%): pale yellow wax; $R_f = 0.4$ (EtOAc/*n*-hexane 4/6); 1H NMR (benzene- d_6) δ 1.222 (dd, H_{6endo} , $J_{6en-6ex} = 12.3$ Hz, $J_{6en-7} = 9.3$ Hz), 1.842 (dt, H_{6exo} , $J_{6ex-5} = J_{6ex-7} = 6.3$ Hz, $J_{6ex-6en} = 12.3$ Hz), 1.956 (s, 3 H), 1.9-2.0 (m, H_7), 2.879 (dd, H_5 , $J_{5-4} = 5.4$ Hz, $J_{5-6ex} = 6.0$ Hz), 3.75 (s, H_1), 6.12 (d, H_4 , $J_{4-5} = 5.4$ Hz), 7.1-7.2 (m, 3 H), 7.3-7.4 (m, 2 H); ^{13}C NMR (benzene- d_6) δ 27.91, 34.56, 37.12, 61.42, 76.07, 116.64, 121.55, 128.91, 128.936, 134.56, 137.05, 146.20, 193.19. **4d** (0.47 g, 16%): pale yellow solid; mp 117 °C, $R_f = 0.26$ (EtOAc/*n*-hexane 8/2); 1H NMR (benzene- d_6) δ 1.417 (dd, H_{6endo} , $J_{6en-7} = 3.3$ Hz, $J_{6en-6ex} = 12.3$ Hz), 1.64 (qd, H_{6exo} , $J_{6ex-6en} = 12.3$ Hz, $J_{6ex-7} = 10.5$ Hz, $J_{6x-5} = 5.7$ Hz), 1.746 (s, 3 H), 2.518 (qd, H_7 , $J_{7-1} = 7.2$ Hz, $J_{7-6ex} = 10.8$ Hz, $J_{7-6en} = 3.3$ Hz), 2.807 (t, H_5 , $J_{5-4} = J_{5-6ex} = 5.7$ Hz), 3.44 (d, H_1 , $J_{1-7} = 7.5$ Hz), 6.28 (d, H_4 , $J_{4-5} = 5.4$ Hz), 7.05-7.20 (m, 3 H), 7.43-7.58 (m, 2 H); ^{13}C NMR (benzene- d_6) δ 26.04, 33.91, 37.31, 61.35, 73.43, 119.12, 128.29, 128.30, 128.53, 133.59, 138.43, 146.08, 193.57.
- d. **4 β -Butyl-8-methyl-2-oxo-3 α -phenyl-8-azabicyclo[3.2.1]octane-6-exo-carbonitrile (7a).** To a cooled (-78 °C) mixture of *n*-butylmagnesium bromide (1.05 mL, 1.01 mmol, 0.96 M in ether), HMPA (0.35 mL, 2.01 mmol) and CuBr.Me₂S (8.6 mg, 0.04 mmol) was added dropwise a mixture of **4a** (200 mg, 0.84 mmol) and trimethylsilyl chloride (0.21 mL, 1.68 mmol) in dry THF (10 mL). After 1 h the reaction was quenched with a 20% solution of NH₄OH (20 mL) and extracted with EtOAc (30 mL). The organic phase was washed with

brine (30 mL), dried and concentrated under reduced pressure. The crude mixture containing the silyl enol ether intermediate was diluted with MeOH (5 mL) and potassium fluoride was added (24 mg, 0.84 mmol). The resulting solution was stirred at 25 °C for 5 min then concentrated under reduced pressure and the crude mixture purified by flash chromatography on silica gel using EtOAc/*n*-hexane as eluant to afford the title compound (220 mg, 88%) as a wax: $R_f = 0.8$ (EtOAc/*n*-hexane 1/1); ^1H NMR (CD_3OD) δ 0.82 (t, 3 H, $J = 7.2$ Hz), 1.1-1.35 (m, 3 H), 1.37-1.15 (m, 4 H), 1.5-1.7 (m, H_4), 2.314 (dd, $\text{H}_{7\text{en}}$, $J_{7\text{en}-7\text{ex}} = 13.5$ Hz, $J_{7\text{en}-6} = 9.9$ Hz), 2.573 (s, 3 H), 2.66 (dt, $\text{H}_{7\text{ex}}$, $J_{7\text{ex}-7\text{en}} = 13.8$ Hz, $J_{7\text{ex}-6} = 7.2$ Hz), 3.06 (dd, H_6 , $J_{6-7\text{ex}} = 6.9$ Hz, $J_{6-7\text{en}} = 9.6$ Hz), 3.55 (d, H_3 , $J_{3-4} = 8.7$ Hz), 3.674 (s, H_5), 3.76 (d, H_1 , $J_{1-7\text{ex}} = 7.2$ Hz), 6.95-7.10 (m, 2 H), 7.2-7.4 (m, 3 H); ^{13}C NMR (benzene- d_6) δ 14.35, 23.25, 29.16, 33.47, 33.50, 34.73, 40.74, 48.82, 56.82, 72.53, 73.08, 123.03, 127.64, 128.90, 130.42, 131.24, 138.19, 209.46; IR (film) 2955, 2234, 1723, 1453 cm^{-1} .

15

Example 2. 4 β -Butyl-2 α -hydroxy-8-methyl-3 α -phenyl-8-

azabicyclo[3.2.1]octane -6-endo-carbonitrile (8b). Using a procedure similar to that described in Example 1, except replacing the compound 7a used therein with compound 7b, the title compound was obtained (95%) as a white solid: $R_f =$

0.4 (EtOAc/*n*-hexane 1/1); ^1H NMR (benzene- d_6) δ 0.797 (t, 3 H, $J = 7.2$ Hz), 0.903 (bs, OH), 1.0-1.4 (m, 6 H), 1.631 (qd, $\text{H}_{7\text{ex}}$, $J_{7\text{ex}-6} = 12$ Hz, $J_{7\text{ex}-7\text{en}} = 13.5$ Hz, $J_{7\text{ex}-1} = 7.5$ Hz), 1.735 (s, 3 H), 2.387 (dd, H_4 , $J_{4-3} = 11.4$ Hz, $J_{4-1} = 9.6$ Hz), 2.538 (dt, H_6 , $J_{6-5} = J_{6-7\text{en}} = 6.3$ Hz, $J_{6-7\text{ex}} = 12.0$ Hz), 2.757 (dd, $\text{H}_{7\text{en}}$, $J_{7\text{en}-7\text{ex}} = 13.5$ Hz, $J_{7\text{en}-6} = 6.3$ Hz), 2.813 (d, H_5 , $J_{5-6} = 6.0$ Hz), 2.90 (dd, H_3 , $J_{3-2} = 5.4$ Hz, $J_{3-4} = 12.0$ Hz), 2.972 (dd, H_1 , $J_{1-2} = 8.2$ Hz, $J_{1-7\text{ex}} = 7.3$ Hz), 3.892 (qd, H_2 , $J_{2-\text{OH}} = 2.1$ Hz, $J_{2-1} = 8.1$ Hz, $J_{2-3} = 5.1$ Hz), 6.98-7.20 (m, 5 H); ^{13}C NMR (benzene- d_6) δ 14.16, 22.98, 24.553, 28.59, 30.05, 34.56, 38.68, 41.02, 47.37, 65.31, 68.27, 70.15, 121.73, 126.97, 128.92, 130.19, 139.78; MS, m/z (%): 298 (M^+ , 14), 255 (30), 241 (8), 177 (10), 137 (29), 82 (52), 42 (100).

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The intermediate compound 7b was prepared as follows.

a. **4 β -Butyl-8-methyl-2-oxo-3 α -phenyl-8-azabicyclo[3.2.1]octane-6-endo-carbonitrile (7b).** Using a procedure similar to that described in Example

1, sub-part f, except replacing the compound **4a** used therein with compound **4b**, compound **7b** was prepared (95%) as a colorless oil: $R_f = 0.6$ (EtOAc/*n*-hexane); ^1H NMR (benzene- d_6) δ 0.721 (t, 3 H, $J = 6.9$ Hz), 1.0-1.43 (m, 6 H), 1.522 (s, 3 H), 1.68-1.88 (m, $\text{H}_{7\text{endo}}$ and $\text{H}_{7\text{exo}}$), 2.227 (td, H_4 , $J_{4,3} = J_{4,1'} = 9.3$ Hz, $J_{4,1''} = 3.0$ Hz), 2.347 (dt, H_6 , $J_{6,5} = J_{6,7\text{en}} = 6.3$ Hz, $J_{6,7\text{ex}} = 11.7$ Hz), 2.85 (d, H_5 , $J_{5,6} = 6.3$ Hz), 2.967 (d, H_1 , $J_{1,7\text{en}} = 7.2$ Hz), 3.442 (d, H_3 , $J_{3,4} = 9.6$ Hz), 7.0-7.2 (m, 5 H); ^{13}C NMR (CDCl_3) δ 13.86, 22.41, 28.66, 29.44, 32.084, 33.95, 40.16, 40.54, 56.06, 68.30, 71.65, 120.29, 127.25, 128.58, 129.74, 136.78, 210.82; IR (film) 2956, 2930, 2235, 1724, 1462, 1105 cm^{-1} .

10

Example 3. 2 β -Butyl-8-methyl-3 α -phenyl-8-azabicyclo[3.2.1]octane-6-exo-carbonitrile (9a).

A solution of **14a** (20 mg, 0.046 mmol), Bu_3SnH (0.02 mL, 0.069 mmol) and AIBN (1.5 mg, 0.01 mmol) in toluene (2 mL) was purged with argon. The reaction flask was placed in a preheated oil bath at 60 $^\circ\text{C}$ and then heated from 60 to 90 $^\circ\text{C}$ over 15 min. After concentration under reduced pressure, the crude residue was purified by flash chromatography on silica gel using EtOAc/*n*-hexane as eluant to afford the title compound (9 mg, 70%) as a colorless oil; $R_f = 0.80$ (EtOAc/*n*-hexane 7/3); ^1H NMR (CDCl_3) δ 0.75 (t, 3 H, $J = 7.2$ Hz), 0.7-0.95 (m, 2 H), 1.04-1.30 (m, 3 H), 1.36-1.56 (m, 2 H), 1.66-1.76 (m, 1 H), 2.18 (dd, $\text{H}_{6\text{endo}}$, $J_{6\text{en}-7} = 9.6$ Hz, $J_{6\text{en}-6\text{ex}} = 13.2$ Hz), 2.12-2.24 (m, 1 H), 2.48-2.59 (m, 1 H), 2.53 (s, 3 H), 2.82 (dt, 1 H, $J = 5.1$ Hz, $J = 13.2$ Hz), 2.99 (dd, H_7 , $J_{7,6\text{en}} = 5.7$ Hz, $J_{7,6\text{ex}} = 9.6$ Hz), 3.44-3.54 (m, H_5), 3.66 (s, H_1), 7.05-7.35 (m, 5 H).

The intermediate compound **14a** was prepared as follows.

- 25 a. **4 β -Butyl-8-methyl-2 α -(phenoxythiocarbonyloxy)-3 α -phenyl-8-azabicyclo[3.2.1]octane-6 β -carbonitrile (14a).** To a solution of alcohol **8a** (54 mg, 0.18 mmol) in THF (5 mL) at -78 $^\circ\text{C}$ was added *n*-BuLi (0.072 mL, 0.18 mmol, 2.5 M in hexane), followed immediately by phenyl thionochloroformate (0.038 mL, 0.27 mmol). After 1 h, the reaction was quenched with a saturated solution of NaHCO_3 (20 mL) and extracted with ether (2 x 20 mL). The collected organic phase was dried, concentrated under reduced pressure and the crude mixture purified by flash chromatography on silica gel using EtOAc/*n*-

hexane as eluant to afford compound **14a** (30 mg, 40%) as a colorless oil: R_f = 0.8 (EtOAc/*n*-hexane 2/8); ^1H NMR (CDCl_3) δ 0.83 (t, 3 H, J = 6.6 Hz), 1.2-1.5 (m, 6 H), 1.62-1.8 (m, H_4), 2.25-2.50 (m, $\text{H}_{7\text{endo}}$ and $\text{H}_{7\text{exo}}$), 2.57 (s, 3 H), 2.77 (t, H_6 , J = 8.1 Hz), 3.07 (dd, H_3 , J = 4.8 and 10.8 Hz), 3.50 (bs, H_5), 3.98 (bt, H_1 , J = 6.6 Hz), 5.75 (dd, H_2 , J = 5.1 and 8.7 Hz), 6.84 (d, 2 H, J = 7.8 Hz), 7.1-7.4 (m, 8 H); ^{13}C NMR (CDCl_3) δ 13.95, 22.62, 28.34, 28.64, 33.79, 34.12, 41.95, 44.55, 46.07, 64.15, 71.60, 76.58, 71.00, 77.42, 83.32, 121.67, 123.51, 126.62, 126.91, 128.29, 129.46, 129.76, 138.00, 153.05, 194.33.

10 **Example 4.** **2β -Butyl-8-methyl-3-phenyl-8-azabicyclo[3.2.1]octane-6-exo-carbonitrile (9a and 13a).**

A mixture of **10a** (80 mg, 0.30 mmol) and a catalytic amount of 10% Pd/C in MeOH (7 mL) was hydrogenated under 30 psi of H_2 at 25 °C for 24 h. Filtration through a pad of celite and concentration under reduced pressure afforded a mixture containing the two isomers which was purified by preparative thin layer chromatography on silica gel using EtOAc/*n*-hexane as eluant to afford the title compounds: **13a** (30 mg, 37%): colorless oil; R_f = 0.85 (EtOAc/*n*-hexane 7/3); ^1H NMR (CDCl_3) δ 0.82 (t, 3 H, J = 6.6 Hz), 0.9-1.4 (m, 8 H), 2.03 (dd, $\text{H}_{6\text{endo}}$, $J_{6\text{en-7}} = 9.3$ Hz, $J_{6\text{en-6ex}} = 12.9$ Hz), 2.3-2.6 (m, 3 H), 2.49 (s, 3 H), 2.75 (t, H_7 , J = 8.1 Hz), 3.41 (s, H_1), 3.47 (bt, H_5 , J = 7.8 Hz), 7.1-7.3 (m, 5 H); ^{13}C NMR (CDCl_3) δ 13.93, 22.71, 28.94, 33.00, 34.02, 36.23, 39.08, 40.09, 42.05, 51.47, 60.82, 71.52, 123.99, 126.21, 127.89, 128.35, 144.45; MS, m/z (%): 282 (M^+ , 12), 239 (13), 225 (64), 172 (12), 107 (32), 42 (100); and **9a** (50 mg, 63%): colorless oil; R_f = 0.80 (EtOAc/*n*-hexane 7/3); ^1H NMR (CDCl_3) δ 0.75 (t, 3 H, J = 7.2 Hz), 0.7-0.95 (m, 2 H), 1.04-1.30 (m, 3 H), 1.36-1.56 (m, 2 H), 1.66-1.76 (m, 1 H), 2.18 (dd, $\text{H}_{6\text{endo}}$, $J_{6\text{en-7}} = 9.6$ Hz, $J_{6\text{en-6ex}} = 13.2$ Hz), 2.12-2.24 (m, 1 H), 2.48-2.59 (m, 1 H), 2.53 (s, 3 H), 2.82 (dt, 1 H, J = 5.1 Hz, J = 13.2 Hz), 2.99 (dd, H_7 , $J_{7-6\text{en}} = 5.7$ Hz, $J_{7-6\text{ex}} = 9.6$ Hz), 3.44-3.54 (m, H_5), 3.66 (s, H_1), 7.05-7.35 (m, 5 H); ^{13}C NMR (CDCl_3) δ 13.98, 22.60, 26.42, 29.60, 30.58, 32.21, 32.55, 36.53, 42.68, 45.91, 63.02, 71.28, 124.25, 126.21, 127.58, 127.91, 128.26, 141.95; MS, m/z (%): 282 (M^+ , 12), 239 (13), 225 (11), 172 (20), 107 (57), 42 (100).

The intermediate compound **10a** was prepared as follows.

- a. **2-Hydroxy-8-methyl-3-phenyl-8-azabicyclo[3.2.1]octane-3-ene-6-exo-carbonitrile (11a).** Enone **4a** (200 mg, 0.84 mmol) was dissolved in a solution of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (340 mg, 0.92 mmol) in MeOH (2.3 mL), then NaBH_4 (32 mg, 0.84 mmol) was added portionwise. This mixture was stirred at 25 °C for 5 min then diluted with water (30 mL) and extracted with EtOAc (2 x 30 mL). The collected organic phases were dried and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel using EtOAc/n-hexane as eluant to obtain a mixture of the two alcohols (200 mg, 98%) as a white foam: $R_f = 0.8$ (EtOAc/n-hexane 8/2). 2α isomer: $^1\text{H NMR}$ (CDCl_3) δ 1.83 (bs, OH), 2.32 (qd, $\text{H}_{7\text{ex}}$, $J = 3.3, 7.2$ and 14.1 Hz), 2.66 (s, 3 H), 2.77 (dd, $\text{H}_{7\text{en}}$, $J = 9.6$ and 13.8 Hz), 3.02 (dd, H_6 , $J = 3.3$ and 9.6 Hz), 3.68 (t, H_1 , $J = 6.0$ Hz), 3.78 (d, H_5 , $J = 5.4$ Hz), 5.15 (d, H_2 , $J = 5.1$ Hz), 6.11 (d, H_4 , $J = 5.4$ Hz), 7.24-7.40 (m, 5 H); MS, m/z (%): 240 (M^+ , 4), 186 (2), 170 (28), 154 (3), 128 (30), 85 (4), 57 (100). 2β isomer: $^1\text{H NMR}$ (CDCl_3) δ 1.70 (bs, OH), 1.95 (dd, $\text{H}_{7\text{en}}$, $J = 9.9$ and 14.1 Hz), 2.55 (qd, $\text{H}_{7\text{ex}}$, $J = 3.9, 8.1$ and 14.1 Hz), 2.90 (dd, H_6 , $J = 3.6$ and 9.9 Hz), 3.68 (d, H_1 , $J = 8.1$ Hz), 3.91 (d, H_5 , $J = 6.0$ Hz), 4.13 (s, H_2), 6.33 (d, H_4 , $J = 6.0$ Hz), 7.24-7.45 (m, 5 H); MS, m/z (%): 240 (M^+ , 2), 186 (4), 170 (30), 115 (2), 85 (3), 57 (100).
- b. **2-Acetoxy-8-methyl-3-phenyl-8-azabicyclo[3.2.1]oct-3-ene-6-exo-carbonitrile (12a).** To a solution of **11a** (200 mg, 0.83 mmol) in pyridine (2 mL) was added acetic anhydride (0.31 mL, 3.33 mmol). The resulting solution was stirred at 25 °C for 15 h then concentrated under reduced pressure, diluted with EtOAc (30 mL) and washed with NH_4Cl (2 x 20 mL), dried and concentrated under reduced pressure to afford a crude mixture of the two isomers that were separated by flash chromatography on silica gel using EtOAc/n-hexane as eluant. 2α -Acetoxy isomer (180 mg, 76%): white solid; mp 107-109 °C; $R_f = 0.6$ (EtOAc/n-hexane 1/1); $^1\text{H NMR}$ (CDCl_3) δ 1.91 (s, 3 H), 2.34 (qd, $\text{H}_{7\text{ex}}$, $J = 3.0, 6.9$ and 13.8 Hz), 2.64 (dd, $\text{H}_{7\text{en}}$, $J = 9.6$ and 13.8 Hz), 2.70 (s, 3 H), 3.08 (dd, H_6 , $J = 3.3, 9.6$ Hz), 3.76 (t, H_1 , $J = 6.0$ Hz), 3.81 (d, H_5 , $J = 5.4$ Hz), 6.25 (d, H_4 , $J = 5.4$ Hz), 6.30 (d, H_2 , $J = 5.1$ Hz), 7.15-7.22 (m, 2 H), 7.27-7.36 (m, 3

- H), ^{13}C NMR (CDCl_3) δ 20.86, 28.92, 33.61, 37.23, 60.73, 63.60, 69.37, 122.37, 125.62, 128.03, 128.32, 128.43, 136.41, 136.62, 170.49; MS, m/z (%): 282 (M^+ , 5), 223 (10), 182 (7), 170 (100), 128 (9), 115 (9); and 2 β -Acetoxy isomer (50 mg, 21%): white solid; mp 134-137 °C; R_f = 0.55 (EtOAc/*n*-hexane 1/1); ^1H NMR (CDCl_3) δ 1.97 (s, 3 H), 2.03 (dd, $\text{H}_{7\text{en}}$, J = 9.3 and 13.8 Hz), 2.56 (qd, $\text{H}_{7\text{ex}}$, J = 3.3, 7.5 and 13.8 Hz), 2.61 (s, 3 H), 2.88 (dd, H_6 , J = 3.3 and 9.3 Hz), 3.65 (d, H_1 , J = 7.5 Hz), 4.0 (d, H_5 , J = 5.4 Hz), 5.42 (s, H_2), 6.40 (d, H_4 , J = 5.7 Hz), 7.24-7.57 (m, 5 H); ^{13}C NMR (CDCl_3) δ 20.93, 31.13, 32.30, 38.37, 62.84, 64.03, 68.86, 122.25, 125.56, 128.36, 128.62, 128.84, 134.23, 136.32, 170.53; MS, m/z (%): 282 (M^+ , 3), 223 (4), 186 (3), 170 (100), 154 (5), 128 (40), 127 (3), 115 (3), 57 (76).

- c. **2 β -Butyl-8-methyl-3-phenyl-8-azabicyclo[3.2.1]oct-3-ene-6-exo-carbonitrile (10a).** To a suspension of CuCN (4.0 mg, 0.045 mmol) in dry ether (2 mL) at -7 °C was added *n*-BuMgBr (0.45 mL, 0.45 mmol, 1.0 M in ether). After 10 minutes, a solution of compound **12a** (60 mg, 0.22 mmol) in dry ether (3 mL) was added dropwise and the resulting mixture stirred at 25 °C for 1.5 h, diluted with ether (20 mL) and the organic phase washed with a saturated solution of NH_4Cl (2 x 20 mL), dried and concentrated under reduced pressure. The crude mixture was purified by flash chromatography on silica gel using EtOAc/*n*-hexane as eluant to afford compound **10a** (48 mg, 80%) as a colorless oil; R_f = 0.7 (EtOAc/*n*-hexane 3/7); ^1H NMR (benzene- d_6) δ 0.76 (t, 3 H, J = 6.6 Hz), 1.0-1.4 (m, 5 H), 1.6-1.1.7 (m, H_2), 1.71 (dd, $\text{H}_{6\text{en}}$, J = 9.0 and 12.0 Hz), 2.0-2.12 (m, $\text{H}_{6\text{ex}}$), 2.21 (s, 3 H), 2.118-2.3 (m, H_7), 2.90 (t, H_5 , J = 5.4 Hz), 3.51 (s, H_1), 5.58 (d, H_4 , J = 5.4 Hz), 7.04-7.20 (m, 5 H); ^{13}C NMR (CDCl_3) δ 13.94, 22.61, 30.17, 30.70, 31.85, 37.22, 41.94, 47.52, 62.16, 70.10, 123.62, 125.83, 127.52, 128.32, 128.47, 138.17, 139.39; MS, m/z (%): 280 (M^+ , 3), 237 (2), 170 (9), 119 (100), 107 (17), 91 (14).

- Example 5.** **2 β -Butyl-7 α -fluoro-8-methyl-3 β -phenyl-8-azabicyclo[3.2.1]octane (59).**

To a mixture of **58** (30 mg, 0.072 mmol) and Na_2HPO_4 in HPLC grade methanol was added Na-Hg (82 mg) and stirred at room temperature for 3 hours.

The resultant mercury was filtered, and the filtrate was concentrated. The residue was dissolved in dichloro methane and washed with water, brine, dried and concentrated. Purification using PTLC afforded the title compound **59** (14.0 mg, 70%); ¹H-NMR (**10**): (CDCl₃, 300 Mhz): δ 0.78 (t, 3H, *J* = 7.0), δ 1.03-1.40 (m, 8H), δ 1.65 (ddd, 1H, *J* = 26.1, 14.4, 2.4), δ 2.16 (s, 3H), δ 2.36 (s, 3H), δ 2.30-2.80 (m, 3H), δ 3.13 (d, 1H, *J* = 6.3), δ 19 (t, 1H, *J* = 8.1), δ 5.30-5.60 (dddd, 1H, *J* = 57.6, 9.3, 6.3, 2.7), δ 7.25 (brm, 5H).

The intermediate compound **58** was prepared as follows.

a. **8-Methyl-2-oxo-3-phenyl-8-azabicyclo[3.2.1]oct-3-ene-6α-fluoro-6β-phenylsulfone (53)**. A mixture of phenyl (1-fluorovinyl)sulfone (0.73 g, 3.986 mmol) and compound **3** (0.82 g, 4.385 mmol) in dry acetonitrile was refluxed for 20 hours under nitrogen atmosphere. The solvent was removed under reduced pressure and the residue was purified by column chromatography to give compound **53**: 0.75 g (69%), compound **54**: 0.054 g (5%), and compound **55**: 0.087 g (8%); ¹H-NMR (**53**): (CDCl₃, 300 Mhz): δ 1.92 (dd, 1H, *J* = 24.0, 15.3), δ 2.60 (s, 3H), δ 3.28 (ddd, 1H, *J* = 22.6, 15.0, 7.5), δ 3.80 (d, 1H, *J* = 7.5), δ 4.60 (d, 1H, *J* = 5.4), δ 6.80 (dd, 1H, *J* = 1.5, 5.4), δ 7.34 (s, 5H), δ 7.60-8.06 (m, 5H).

b. **2-Acetoxy-8-methyl-3-phenyl-8-azabicyclo[3.2.1]oct-3-ene-6α-fluoro-6β-phenylsulfone (mixture 56)**. To a solution of **53** (0.60 g, 1.6 mmol) in MeOH/DCM (20 ml, 1:1 v/v) was added CeCl₃·7H₂O (0.60 g, 1.6 mmol) and the mixture was stirred at room temperature for 30 minutes. Then NaBH₄ (0.06 g, 1.65 mmol) was added in portions and continued stirring for further 30 minutes. Methanol was removed under reduced pressure and the residue partitioned between aq. NH₄Cl and dichloro methane. The organic layer washed with water, brine, dried (Na₂SO₄) and concentrated under reduced pressure. Without any further purification, the compound was carried for next reaction. The crude alcohol (0.60 g, 1.6 mmol) was stirred with 10 ml of pyridine/acetic anhydride (2:1 v/v) for 15 hours at room temperature. The excess pyridine and acetic anhydride were removed under reduced pressure. The residue was diluted with ethyl acetate and washed with sat. NaHCO₃, water and dried (Na₂SO₄). The solvent was removed under reduced pressure and the residue was purified by

column chromatography to afford a mixture of diastereomers **56** in 90% yield (0.60 g). The mixture was used in sub-part c, without further purification.

c. **2 β -Butyl-8-methyl-3-phenyl-8-azabicyclo[3.2.1]oct-3-ene-7 α -fluoro-7 β -phenylsulfone (57)**. Dry CuCN (42 mg) was suspended in dry diethyl ether under inert atmosphere and cooled to -15°C (the temperature was measured externally). n-BuMgBr (2.0 ml of 2 M solution in diethyl ether) was added dropwise and the solution was stirred for 30 minutes. A solution of **56** (420 mg, 1.01 mmol) was added through canula by maintaining the temperature at -15°C. Once the addition was complete, the mixture was warmed to room temperature and stirred for 1 hour (the reaction mixture turned dark brown). The reaction mixture was diluted with diethyl ether and washed with NH₄Cl/NH₄OH mixture (1:1), NaCl solution and dried (Na₂SO₄). The solvent was removed under reduced pressure and the residue was purified by column chromatography to give 0.34 g (80%) of compound **57** as a colorless syrup; GCMS: 413 (M⁺), 272 (base peak); ¹H-NMR: (CDCl₃, 300 Mhz): δ 0.82 (t, 3H, *J* = 7.2), δ 1.10-1.40 (m, 6H), δ 1.55-1.57 (brm, 1H), δ 2.00 (dd, 1H, *J* = 21.3, 14.1), δ 2.70 (s, 3H), δ 2.92 (ddd, 1H, *J* = 26.2, 14.4, 5.7), δ 3.54 (t, 1H, *J* = 5.7), δ 3.95 (brs, 1H), δ 5.96 (d, 1H, *J* = 5.7), δ 7.26 (brm, 5H), δ 7.56-8.06 (m, 5H).

d. **2 β -Butyl-8-methyl-3 β -phenyl-8-azabicyclo[3.2.1]octane-7 α -fluoro-7 β -phenylsulfone (58)**. To a solution of **57** (0.30 g, 0.726 mmol) in ethyl acetate (20 ml) PtO₂ (10 mg) was added and stirred for 3 hours under H₂ pressure. The catalyst was filtered off and the filtrate was concentrated to give crude **58** as yellow color solid. Recrystallization gave **58** (270 mg, 90%) as colorless crystals; M.P. 173°C; GCMS: 415 (M⁺), 100 (base peak); ¹H NMR: (CDCl₃, 300 Mhz): δ 0.70 (t, 3H, *J* = 7.0), δ 0.85-1.41 (m, 7H), δ 1.78 (dd, 1H, *J* = 21.0, 14.1), δ 2.00 (m, 1H), δ 2.30 (m, 1H), δ 2.58 (m, 1H), δ 2.56 (s, 3H), δ 2.90 (ddd, 1H, *J* = 30.6, 14.1, 5.1), δ 3.43 (brm, 1H), δ 3.52 (d, 1H, *J* = 6.0), δ 7.10-8.06 (m, 10H).

30

Example 6. **2 β -Butyl-7 β -fluoro-8-methyl-3 β -phenyl-8-azabicyclo[3.2.1]octane (60)**.

The title compound was isolated from the chromatography of Example 5 gave the title compound **60** (2.0 mg, 10%); $^1\text{H-NMR}$: (CDCl_3 , 300 Mhz): δ 0.83 (t, 3H, $J = 7.2$), δ 1.03-1.40 (m, 9H), δ 1.62 (brs, 2H), δ 2.06 (ddd, 1H, $J = 21.6$, 18.0, 6.6), δ 2.38-2.80 (m, 3H), δ 2.58 (s, 3H), δ 3.20 (d, 1H, $J = 16.5$), δ 3.48 (t, 1H, $J = 8.1$), δ 5.05-5.26 (dd, 1H, $J = 56.1$, 6.6), δ 7.20 (brm, 5H).

Example 7. Synthesis of 8-methyl-2-oxo-3-phenyl-8-azabicyclo[3.2.1]oct-3-ene-6-phenylsulfone and 8-methyl-2-oxo-3-phenyl-8-azabicyclo[3.2.1]oct-3-ene-7-phenylsulfone (5a-c). To a solution of **3** (0.59 g, 3.17 mmol) in acetonitrile (20 mL) was added phenyl vinylsulfone (1.07 g, 6.34 mmol). The resulting solution was refluxed under nitrogen for 1 h then concentrated under reduced pressure. The three isomers **5a-c** present in the crude mixture were separated by flash chromatography on silica gel using EtOAc/n-hexane as eluant. **5a** (60%): pale yellow solid; $R_f = 0.8$ (EtOAc/n-hexane 1/1); $^1\text{H NMR}$ (CDCl_3) δ 2.01 (dd, $\text{H}_{7\text{endo}}$, $J_{7\text{en}-7\text{ex}} = 14.1$ Hz, $J_{7\text{en}-6} = 9.0$ Hz), 2.485 (s, 3 H), 2.818 (qd, $\text{H}_{7\text{exo}}$, $J_{7\text{ex}-6} = 4.5$ Hz, $J_{7\text{ex}-1} = 7.5$ Hz, $J_{7\text{ex}-7\text{en}} = 12.3$ Hz), 3.668 (dd, H_6 , $J_{6-7\text{ex}} = 4.5$ Hz, $J_{6-7\text{en}} = 9.0$ Hz), 3.714 (d, H_1 , $J_{1-7\text{ex}} = 7.5$ Hz), 4.412 (d, H_5 , $J_{5-4} = 5.4$ Hz), 6.985 (d, H_4 , $J_{4-5} = 5.4$ Hz), 7.34 (bs, 5 H), 7.55-7.63 (m, 2 H), 7.64-7.72 (m, 1 H), 7.91-7.98 (m, 2 H); $^{13}\text{C NMR}$ (CDCl_3) δ 27.76, 34.74, 61.00, 67.70, 70.29, 128.16, 128.29, 128.62, 128.66, 129.28, 133.28, 133.95, 138.29, 138.92, 141.08, 196.85. **5b** (16 %): pale yellow foam; $R_f = 0.4$ (EtOAc/n-hexane 8/2), $^1\text{H NMR}$ (CDCl_3) δ 2.15 (dd, $\text{H}_{7\text{endo}}$, $J_{7\text{en}-7\text{ex}} = 14.1$ Hz, $J_{7\text{en}-6} = 6.9$ Hz), 2.435 (s, 3 H), 2.56 (qd, $\text{H}_{7\text{exo}}$, $J_{7\text{ex}-6} = 9.6$ Hz, $J_{7\text{ex}-7\text{en}} = 13.8$ Hz, $J_{7\text{ex}-1} = 8.1$ Hz), 3.73 (d, H_1 , $J_{1-7\text{ex}} = 7.8$ Hz), 4.15 (m, H_6), 4.217 (t, H_5 , $J_{5-4} = J_{5-6} = 5.1$ Hz), 7.20 (d, H_4 , $J_{4-5} = 5.1$ Hz), 7.32-7.43 (m, 3 H), 7.47-7.53 (m, 2 H), 7.54-7.62 (m, 2 H), 7.64-7.72 (m, 1 H), 7.87-7.94 (m, 2 H); $^{13}\text{C NMR}$ (CDCl_3) δ 27.16, 36.65, 62.07, 67.13, 71.10, 127.90, 128.13, 128.25, 128.62, 129.5, 134.01, 139.23, 139.77, 141.60, 196.38. **5c** (16%): pale yellow foam; $R_f = 0.2$ (EtOAc/n-hexane 1/1); $^1\text{H NMR}$ (CDCl_3) δ 2.2 (dd, $\text{H}_{6\text{endo}}$, $J_{6\text{en}-6\text{ex}} = 13.2$ Hz, $J_{6\text{en}-7} = 9.0$ Hz), 2.563 (s, 3 H), 2.795 (dt, $\text{H}_{6\text{exo}}$, $J_{6\text{ex}-5} = J_{6\text{ex}-7} = 6.6$ Hz, $J_{6\text{ex}-6\text{en}} = 12.9$ Hz), 3.534 (t, H_7 , $J_{7-6\text{ex}} = J_{7-6\text{en}} = 8.1$ Hz), 3.9-4.2 (m, H_5 and H_1), 7.034 (d, H_4 , $J_{4-5} = 5.4$ Hz), 7.324 (bs, 5 H), 7.55-7.63 (m, 2 H), 7.64-7.72 (m, 1 H), 7.92-7.99 (m, 2 H); $^{13}\text{C NMR}$

(CDCl₃) δ 30.88, 36.60, 61.35, 64.40, 71.89, 128.15, 128.23, 128.33, 128.46, 129.46, 133.37, 134.05, 137.05, 138.63, 145.29, 193.61.

Example 8. (1R,5S)-2 β -*n*-Propyl-3 β -phenyltropane (21).

5 A solution of *n*-BuLi (1.20 mL, 2.62 mmol, 1.2 M in hexane) was dissolved in THF (10 mL) and cooled to 0 °C. Ethyltriphenylphosphonium bromide (0.97 g, 2.62 mmol) was added slowly under nitrogen. The resulting yellow-orange solution was stirred at 0 °C for 30 min., and then the cooling bath was removed. The crude aldehyde **18** (0.20 g, 0.87 mmol) was added in THF (2
10 mL), and the reaction mixture was stirred for 15 h at RT, diluted with EtOAc (20 mL) and washed with NH₄Cl (2 X 30 mL). The organic phase was extracted with HCl 10% (3 X 10 mL). The collected aqueous phase was washed with EtOAc (30 mL), neutralized with a saturated solution of NaHCO₃ and extracted with CH₂Cl₂ (2 X 30 mL). The collected organic phase was dried, concentrated
15 under reduced, and the residue was purified by flash chromatography (silica gel, ether/TEA, 9.5/0.5) to afford 0.15 g (71%) of the intermediate olefin as a mixture of the cis and trans isomers.

To a solution of the intermediate olefins (0.15 g) in MeOH (10 mL) was added a catalytical amount of Pt/C 5%. The mixture was stirred at RT for 30
20 min. under a hydrogen atmosphere at 40 psi. The resulting solution was filtered over Celite and evaporated to dryness. The resulting colorless oil was purified by flash chromatography (silica gel, ether/TEA, 9.5/0.5) to afford the 0.13 g (95%) of **21** as a colorless oil: $[\alpha]_D^{25}$ -97° (c=0.5, CH₂Cl₂); ¹H NMR (CDCl₃) δ 0.71 (t, 3H, *J* = 7.2 Hz), 0.78-0.95 (m, 1H), 1.20-1.35 (m, 1H), 1.38-1.56 (m,
25 2H), 1.56-1.75 (m, 3H), 1.97-2.26 (m, 3H), 2.25 (s, 3H), 3.07 (dt, 1H, *J* = 5.1 and 13.2 Hz), 3.12-3.20 (m, 1H), 3.20-3.29 (m, 1H), 7.10-7.35 (m, 5H); ¹³C NMR (CDCl₃) δ 14.2, 20.8, 24.8, 26.4, 29.3, 33.6, 36.4, 42.1, 46.0, 62.0, 64.7, 125.6, 127.8, 128.0, 143.8; MS *m/z* (%) 243 (M⁺, 11), 214 (8), 82 (100).

The intermediate aldehyde **18** was prepared as follows.

30 a. **Methyl (1R,5S)-3 β -phenyltropane-2 β -carboxylate (15).** Compound **15** was prepared from (-)-cocaine by a procedure analogous to that reported by Kozikowski and co-worker (*J. Med. Chem.* 1995, 38, 3086-3093); a colorless oil:

¹H NMR (CDCl₃) δ 1.54-1.78 (m, 3H), 2.02-2.24 (m, 2H), 2.23 (s, 3H), 2.60 (dt, 1H, *J* = 2.7 and 12.6 Hz), 2.92 (t, 1H, *J* = 3.6 Hz), 3.00 (dt, 1H, *J* = 5.1 and 12.6 Hz), 3.33-3.42 (m, 1H), 3.48 (s, 3H), 3.52-3.60 (m, 1H), 7.10-7.30 (m, 5H); ¹³C NMR (CDCl₃) δ 25.2, 25.9, 33.7, 33.9, 42.0, 51.1, 52.8, 62.3, 65.3, 125.8, 127.3, 127.9, 143.0, 172.1. Anal. (C₁₆H₂₁NO₂) C, H, N.

- 5 b. **(1*R*,5*S*)-2β-formyl-3β-phenyltropane (18).** To a solution of **15** (0.50 g, 1.93 mmol) in THF (20 mL) was added portionwise LiAlH₄ (0.15 g, 3.85 mmol). The resulting mixture was stirred at RT for 2 h then a saturated solution of Rochelle salt (30 mL) was added followed by extraction with EtOAc (100 mL).
- 10 The organic phase was washed with brine (100 mL), dried and concentrated under reduced pressure to afford 0.35 g (79%) of the alcohol intermediate as a white solid: ¹H NMR (CDCl₃) δ 1.43-50 (m, 1H), 1.57-1.66 (m, 1H), 1.73 (d, 1H, *J* = 8.1 Hz), 1.67-1.80 (m, 1H), 2.04-2.24 (m, 2H), 2.27 (s, 3H), 2.51 (dt, 1H, *J* = 2.7 and 12.9 Hz), 3.05 (dt, 1H, *J* = 6.0 and 13.2 Hz), 3.28-3.35 (m, 1H),
- 15 3.39 (dd, 1H, *J* = 2.1 and 10.8 Hz), 3.42-3.50 (m, 1H), 3.74 (dd, *J* = 2.1 and 11.1 Hz), 7.10-7.40 (m, 5H); MS *m/z* 231 (M⁺, 12), 200 (14), 172 (12), 82 (100).

Oxalyl chloride (0.10 mL, 1.08 mmol) was dissolved in anhydrous CH₂Cl₂ (10 mL), and the solution was cooled to -78 °C. Dimethyl sulfoxide (0.15 mL, 2.16 mL) was added, after 5 min. the above alcohol (0.25 g, 1.08 mmol) was added in CH₂Cl₂ (5 mL), and stirring was continued for 30 min. The reaction mixture was quenched by adding Et₃N (1.4 mL), and the resulting solution was warmed to RT, diluted with CH₂Cl₂ (30 mL) and washed with NH₄Cl (2 X 30 mL), dried and concentrated under reduced pressure to provide 0.21 g (84%) of **18** as a colorless oil used in the next step without further

25 purification: ¹H NMR (CDCl₃) δ 1.70 (d, 1H, *J* = 8.4 Hz), 1.63-1.78 (m, 1H), 1.91 (dt, 1H, *J* = 3.6 and 12.9), 2.19 (s, 3H), 2.10-2.28 (m, 2H), 2.40-2.56 (m, 2H), 3.18 (dt, 1H, *J* = 5.4 and 13.2 Hz), 3.38-3.45 (m, 1H), 3.48-3.55 (m, 1H), 7.15-7.40 (m, 5H), 9.65 (d, 1H, *J* = 3.0 Hz).

Example 9. (1*R*,5*S*)-2β-*n*-Propyl-3β-(*p*-tolyl)tropane (22).

- 30 Using a procedure similar to that described in Example 8, except replacing the compound **18** used therein with compound **19**, the title compound **22** was prepared as a colorless oil: [α]_D²⁵ -82° (c 0.5, CH₂Cl₂); ¹H NMR (CDCl₃)

δ 0.72 (t, 3H, $J = 7.2$ Hz), 0.80-0.96 (m, 1H), 1.20-1.36 (m, 1H), 1.39-1.56 (m, 2H), 1.56-1.75 (m, 3H), 1.96-2.26 (m, 3H), 2.25 (s, 3H), 2.31 (s, 3H), 3.04 (dt, 1H, $J = 4.8$ and 13.2 Hz), 3.12-3.20 (m, 1H), 3.20-3.29 (m, 1H), 7.02 (d, 2H, $J = 8.1$ Hz), 7.08 (d, 2H, $J = 8.1$ Hz); ^{13}C NMR (CDCl_3) δ 14.1, 20.7, 20.9, 24.8, 26.4, 29.1, 33.7, 35.9, 42.0, 45.9, 62.1, 64.7, 127.6, 128.7, 135.0, 140.5.

The intermediate compound **19** was prepared as follows.

- a. **Methyl (1R,5S)-3 β -(p-tolyl)tropane-2 β -carboxylate (16).** Compound **15** was prepared from (-)-cocaine by a procedure analogous to that reported by Kozikowski and co-worker (*J. Med. Chem.* **1995**, 38, 3086-3093); a colorless oil: ^1H NMR (CDCl_3) δ 1.54-1.78 (m, 3H), 2.00-2.24 (m, 2H), 2.22 (s, 3H), 2.29 (s, 3H), 2.58 (dt, 1H, $J = 2.7$ and 12.3 Hz), 2.89 (t, 1H, $J = 3.6$ Hz), 2.97 (dt, 1H, $J = 4.8$ and 12.9 Hz), 3.32-3.40 (m, 1H), 3.49 (s, 3H), 3.52-3.60 (m, 1H), 7.07 (d, 2H, $J = 7.8$ Hz), 7.14 (d, 2H, $J = 7.8$ Hz); ^{13}C NMR (CDCl_3) δ 21.0, 25.2, 25.9, 33.3, 34.1, 42.0, 51.1, 52.8, 62.3, 65.3, 127.1, 128.6, 135.1, 139.9, 172.2.
- b. **(1R,5S)-2 β -formyl-3 β -(p-tolyl)tropane (19).** Using a procedure similar to that described in Example 8, sub-part b, except replacing the compound **15** used therein with compound **16**, the title compound **19** was prepared as a colorless oil: ^1H NMR (CDCl_3) δ 1.70 (d, 1H, $J = 8.7$ Hz), 1.60-1.78 (m, 1H), 1.89 (dt, 1H, $J = 3.9$ and 12.9), 2.19 (s, 3H), 2.30 (s, 3H), 2.10-2.33 (m, 2H), 2.39-2.53 (m, 2H), 3.14 (dt, 1H, $J = 5.7$ and 12.9 Hz), 3.36-3.45 (m, 1H), 3.46-3.55 (m, 1H), 7.10 (br s, 4H), 9.66 (d, 1H, $J = 3.3$ Hz).

Example 10. (1R,5S)-2 β -n-Butyl-3 β -(p-tolyl)tropane (23).

- Using a procedure similar to that described in Example 8, except replacing the compound **18** used therein with compound **19**, and replacing the ethyl phosphonium salt with the corresponding propyl phosphonium salt, the title compound **23** was prepared as a colorless oil: $[\alpha]_D^{25} -76^\circ$ (c 1.5, CH_2Cl_2); ^1H NMR (CDCl_3) δ 0.74 (t, 3H, $J = 7.2$ Hz), 0.70-0.90 (m, 2H), 1.12-1.30 (m, 3H), 1.39-1.68 (m, 5H), 1.96-2.20 (m, 3H), 2.24 (s, 3H), 2.31 (s, 3H), 3.03 (dt, 1H, $J = 5.1$ and 13.2 Hz), 3.12-3.20 (m, 1H), 3.20-3.28 (m, 1H), 7.03 (d, 2H, $J = 8.1$ Hz), 7.08 (d, 2H, $J = 8.1$ Hz); ^{13}C NMR (CDCl_3) δ 14.2, 21.0, 22.7, 24.8, 26.4, 26.7, 30.1, 33.8, 36.0, 42.1, 46.2, 62.1, 64.7, 127.7, 128.7, 135.0, 140.7; MS m/z

(%) 271 (M^+ , 6), 242 (2), 214 (4), 96(40), 83 (100).

Example 11. (1*R*,5*S*)-2β-*n*-Propyl-3β-(*p*-fluorophenyl)tropane (24).

Using a procedure similar to that described in Example 8, except
5 replacing the compound 18 used therein with compound 20, the title compound
24 was prepared as a colorless oil: $[\alpha]_D^{25}$ -60.4° (*c* 2, $CHCl_3$); 1H NMR ($CDCl_3$)
δ 0.60-0.78 (m, 1H), 0.74 (t, 3H, *J* = 7.2 Hz), 0.80-0.96 (m, 1H), 1.20-1.36 (m,
1H), 1.39-1.76 (m, 5H), 1.95-2.25 (m, 3H), 2.26 (s, 3H), 3.07 (dt, 1H, *J* = 4.8
and 13.2 Hz), 3.14-3.22 (m, 1H), 3.22-3.30 (m, 1H), 6.98 (t, 2H, *J* = 8.7 Hz),
10 7.10 (dd, 2H, *J* = 6.0 and 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 14.1, 20.7, 24.7, 26.3,
29.1, 33.7, 35.6, 42.0, 46.0, 62.0, 64.7, 114.7 (d, J_{C-F} = 83.1 Hz), 128.9 (d, J_{C-F} =
30.6 Hz), 139.2 (d, J_{C-F} = 12.9 Hz), 161.0 (d, J_{C-F} = 970 Hz).

The intermediate compound 20 was prepared as follows.

a. **Methyl (1*R*,5*S*)-3β-(*p*-fluorophenyl)tropane-2β-carboxylate (17).**

15 Compound 17 was prepared from (-)-cocaine by a procedure analogous to that
reported by Kozikowski and co-worker (*J. Med. Chem.* **1995**, 38, 3086-3093); a
colorless oil: 1H NMR ($CDCl_3$) δ 1.56-1.80 (m, 3H), 2.00-2.24 (m, 2H), 2.23 (s,
3H), 2.56 (dt, 1H, *J* = 2.4 and 12.6 Hz), 2.86 (t, 1H, *J* = 3.3 Hz), 2.97 (dt, 1H, *J* =
5.1 and 12.6 Hz), 3.32-3.40 (m, 1H), 3.50 (s, 3H), 3.52-3.60 (m, 1H), 6.95 (t, 2H,
20 *J* = 8.4 Hz), 7.21 (dd, 2H, *J* = 5.7 and 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 25.1, 25.8,
33.2, 34.2, 41.9, 51.1, 52.8, 62.2, 65.2, 114.5 (d, J_{C-F} = 83.1 Hz), 128.7 (d, *J* =
30.6 Hz).

b. **(1*R*,5*S*)-2β-formyl-3β-(*p*-fluorophenyl)tropane (20).** Using a
procedure similar to that described in Example 8, sub-part b, except replacing the
25 compound 15 used therein with compound 17, the compound 20 was prepared as
a colorless oil: 1H NMR ($CDCl_3$) δ 1.74 (d, 1H, *J* = 8.5), 1.64-1.82 (m, 1H), 1.91
(dt, 1H, *J* = 3.8 and 12.7), 2.21 (s, 3H), 2.10-2.33 (m, 2H), 2.39-2.54 (m, 2H), 3.16
(dt, 1H, *J* = 5.7 and 12.9), 3.40-3.48 (m, 1H), 3.50-3.60 (m, 1H), 7.00 (t, 2H, *J* = 8.7),
7.19 (dd, 2H, *J* = 6.0 and 8.4), 9.64 (d, 1H, *J* = 3.2).

30

Example 12. (1*R*, 5*S*)-2β-Phenyl-3α-(*p*-tolyl)tropane (37).

Phosphorous trichloride (61 μL, 0.70 mmol) was added to a solution of

34 (50 mg, 0.12 mmol) in dry DMF (2.00 mL) at 0 °C. After being stirred at 0 °C for 1 h, the reaction was quenched with a saturated solution of NaHCO₃ (20 mL) and extracted with ether (2 x 20 mL). The collected organic phase was washed with water (30 mL), brine (30 mL), dried and concentrated under reduced pressure to afford 30 mg (61%) of the sulfide intermediate as a colorless oil used in the next step without further purification: *R*_f 0.5 (EtOAc/hexane 1/9). ¹H NMR (CDCl₃) δ 1.34 (dt, 1H, *J* = 1.8 and 14.1 Hz), 2.10-2.35 (m, 2H), 2.23 (s, 3H), 2.42 (ddd, 1H, *J* = 6.9, 10.2, and 13.8 Hz), 2.62 (s, 3H), 2.65 (d, 1H, *J* = 10.5 Hz), 2.98-3.12 (m, 1H), 3.36 (br s, 1H), 3.50-3.60 (m, 1H), 3.70 (t, 1H, *J* = 7.8 Hz), 6.85 (d, 2H, *J* = 7.8 Hz), 6.94 (d, 2H, *J* = 7.8 Hz), 7.02-7.26 (m, 9H); ¹³C NMR (CDCl₃) δ 20.9, 39.0, 39.5, 42.1, 43.2, 52.7, 58.8, 60.5, 75.5, 125.9, 127.2, 127.9, 128.0, 128.7, 129.2, 129.6, 134.4, 135.4, 135.7, 140.9, 146.6.

Raney-Ni was added to a solution of the sulfide (30 mg, 0.07 mmol) in ethanol (4 mL) and the resulting mixture was refluxed for 1 h. Filtration through a pad of celite and concentration under reduced pressure afforded a crude mixture that was purified by flash chromatography on silica gel using ether/Et₃N (9.5/0.5) as eluent to afford 15 mg (73%) of **22** as a colorless oil: [α]_D²⁵ -118° (c 0.3, CH₂Cl₂); ¹H NMR (CDCl₃) δ 1.32 (t, 1H, *J* = 12.3 Hz), 1.50-1.75 (m, 2H), 2.10-2.38 (m, 2H), 2.23 (s, 3H), 2.31 (s, 3H), 2.44 (d, 1H, *J* = 10.8 Hz), 2.42-2.56 (m, 1H), 2.97 (dt, 1H, *J* = 7.2 and 11.4 Hz), 3.27 (d, 1H, *J* = 6.6 Hz), 3.36 (t, *J* = 6.6 Hz), 6.84 (d, 2H, *J* = 7.8 Hz), 6.93 (d, 2H, *J* = 7.8 Hz), 7.02-7.20 (m, 5H); ¹³C NMR (CDCl₃) δ 20.9, 29.7, 29.8, 41.1, 41.3, 43.0, 58.6, 59.5, 68.1, 125.6, 127.3, 127.9, 128.1, 128.6, 135.1, 141.5, 147.6; MS *m/z* (%) 291 (M⁺, 1), 178 (4), 115 (6), 96 (59), 82 (100).

The intermediate compound **34** was prepared as follows.

- a. **1-Methyl-4-(*p*-tolyl)-3-pyridiniumolate (26)**: Using a procedure similar to that described by Kozikowski and co-worker, *J. Org. Chem.* **1997**, 62, 503-509, compound **26** was prepared; mp 185 °C (dec); ¹H NMR (CDCl₃) δ 2.38 (s, 3H), 3.94 (s, 3H), 6.95 (dd, 1H, *J* = 2.1 and 6.0 Hz), 7.24 (d, 2H, *J* = 8.1 Hz), 7.36 (d, 1H, *J* = 6.0 Hz), 7.43 (d, 1H, *J* = 1.8 Hz), 7.89 (d, 2H, *J* = 8.4 Hz).
- b. **N-Methyl (1*S*,5*S*,6*R*,*R*_s)-3-(*p*-tolyl)-6-(*p*-tolylsulphinyl)-8-azabicyclo[3.2.1]oct-3-en-2-one (29)**. A solution of 1-methyl-4-(*p*-tolyl)-3-

pyridiniumolate **26** (1.86 g, 8.37 mmol) and (+)-(R)-*p*-tolyl vinyl sulfoxide (1.07 g, 6.45 mmol) in dioxane (50 mL) was allowed to reflux for 20 hours. The resulting reaction mixture was concentrated under reduced pressure, purified by silica gel flash chromatography, and recrystallized from EtOAc to give the compound **29** as a white solid: $[\alpha]_D^{25} -47^\circ$ (c 0.8, CH₂Cl₂); *R_f* 0.6 (EtOAc); mp 188 °C.

c. ***N*-Methyl (1*S*,5*R*,7*R*,*R*_s)-4β-phenyl-3α-(*p*-tolyl)-6β-(*p*-tolylsulphynyl)-8-azabicyclo[3.2.1]octan-2-one (31).** To a cooled (-78 °C) mixture of PhMgBr (0.55 mL, 1.64 mmol, 3.0 M in ether), HMPA (0.57 mL, 3.28 mmol), and CuBr•Me₂S (14.00 mg, 0.07 mmol) was added dropwise a mixture of **29** (500 mg, 1.37 mmol) and Me₃SiCl (0.35 mL, 2.74 mmol) in dry THF (20 mL). After 1 h, the reaction was quenched with a 20% solution of NH₄OH (20 mL), and the mixture was extracted with EtOAc (30 mL). The organic phase was washed with brine (30 mL), dried, and concentrated under reduced pressure. The crude mixture containing the silyl enol ether intermediate was diluted with MeOH (10 mL), and potassium fluoride was added (160 mg, 2.74 mmol). The resulting solution was stirred at RT for 5 min, then concentrated under reduced pressure. The crude mixture was purified by flash chromatography on silica gel using EtOAc/hexane as eluent to afford 130 mg (22%) of the compound **31** as a pale yellow foam: *R_f* 0.65 (EtOAc/hexane 1/1); ¹H NMR (CDCl₃) δ 2.04 (dd, 1H, *J* = 8.7 and 11.7 Hz), 2.24 (s, 3H), 2.20-2.34 (m, 1H), 2.41 (s, 3H), 2.56 (s, 3H), 3.10 (t, 1H, *J* = 8.4 Hz), 3.75 (d, 1H, *J* = 5.7 Hz), 3.85 (s, 1H), 4.09 (d, 1H, *J* = 8.4 Hz), 6.66 (d, 2H, *J* = 8.1 Hz), 6.99 (d, 2H, *J* = 7.8 Hz), 7.01-7.10 (m, 2H), 7.10-7.20 (m, 3H), 7.30 (d, 2H, *J* = 8.1 Hz), 7.55 (d, 2H, *J* = 8.1 Hz); ¹³C NMR (CDCl₃) δ 21.0, 21.4, 29.0, 39.7, 55.8, 58.2, 68.8, 72.3, 73.1, 76.6, 77.0, 77.2, 77.4, 124.1, 126.8, 127.0, 128.3, 129.0, 129.1, 130.1, 133.1, 136.5, 140.7, 142.0, 143.9, 211.7.

d. **(1*S*,5*R*,7*R*,*R*_s)-2β-phenyl-3α-(*p*-tolyl)-6β-(*p*-tolylsulphynyl)tropane (34).** To a suspension of LAH (22 mg, 0.59 mmol) in dry THF (6 mL) was added a solution of **31** (130 mg, 0.29 mmol) in dry ether (20 mL). The resulting solution was stirred at RT for 1 h, then quenched with a saturated solution of NH₄Cl. The resulting mixture was extracted with ether (2 x 50 mL). The

- combined organic phases were washed with brine (80 mL), dried, and concentrated under reduced pressure. The crude mixture was purified by flash chromatography on silica gel using EtOAc/hexane 6/4 as eluent to afford 120 mg (92%) of the correspondent 2 α -hydroxy derivatives intermediate as a colorless oil: R_f 0.70 (EtOAc/hexane, 8/2); ^1H NMR (CDCl_3) δ 1.32 (br s, 1H), 1.72-1.88 (m, 1H), 2.2 (s, 3H), 2.41 (s, 3H), 2.51 (s, 3H), 2.40-2.60 (m, 1H), 2.70 (d, 1H, $J = 11.4$ Hz), 3.31 (8.1 Hz), 3.42 (dd, 1H, $J = 4.2$ and 10.8 Hz), 3.56 (br s, 1H), 3.69 (t, 1H, $J = 6.6$ Hz), 4.20-4.30 (m, 1H), 6.90-7.10 (m, 9H), 7.29 (d, 2H, $J = 8.1$ Hz), 7.55 (d, 2H, $J = 8.1$ Hz).
- 10 To a solution of diisopropylamine (45 μL , 0.32 mmol) in dry THF (4 mL) was added dropwise at 0 $^\circ\text{C}$ a solution of *n*-BuLi (134 μL , 0.29 mmol, 2.2 M in hexane). The resulting solution was stirred at 0 $^\circ\text{C}$ for 15 min. then cooled at -78 $^\circ\text{C}$ and a solution of the alcohol intermediate (110 mg, 0.25 mmol) in THF (5 mL) was added dropwise followed, after 5 min., by phenyl thionochloroformate
- 15 (68 μL , 0.49 mmol). After 1 h, the reaction was quenched with a saturated solution of NH_4Cl (20 mL), and the mixture was extracted with ether (2 x 20 mL). The collected organic phases were dried and concentrated under reduced pressure, and the crude mixture was purified by flash chromatography on silica gel using EtOAc/hexane as eluent to afford 100 mg of the
- 20 phenoxy(thiocarbonyl)oxy derivative as a colorless oil: R_f 0.7 (EtOAc/hexane 1/1); ^1H NMR (CDCl_3) δ 1.90 (dd, 1H, $J = 8.1$ and 13.2 Hz), 1.95-2.09 (m, 1H), 2.23 (s, 3H), 2.44 (s, 3H), 2.52 (s, 3H), 2.60 (d, 1H, $J = 11.1$ Hz), 3.20 (t, 1H, $J = 7.5$ Hz), 3.5 (br s, 1H), 3.64 (dd, 1H, $J = 5.1$ and 11.1 Hz), 3.90-4.05 (m, 1H), 5.84 (dd, 1H, $J = 4.8$ and 8.7 Hz), 6.76 (d, 2H, $J = 7.5$ Hz), 6.82-7.42 (m, 14H),
- 25 7.56 (d, 2H, $J = 8.1$ Hz).
- A solution of the above intermediate (95 mg), Bu_3SnH (133 μL , 0.49 mmol), and AIBN (16 mg, 0.01 mmol) in toluene (6 mL) was purged with argon. The reaction flask was placed in a preheated oil bath at 60 $^\circ\text{C}$ and then heated to 90 $^\circ\text{C}$ for 1 h. After concentration under reduced pressure, the crude residue was
- 30 purified by flash chromatography on silica gel using EtOAc/hexane as eluent to afford 53 mg (50%) of the compound **34** as a colorless oil: R_f 0.3 (EtOAc/hexane, 3/7); ^1H NMR (CDCl_3) δ 0.90 (t, 1H, $J = 12.3$ Hz), 1.18-1.40

(m, 2H), 1.52 (dd, 1H, $J = 8.1$ and 13.2 Hz), 2.08-2.20 (m, 1H), 2.22 (s, 3H), 2.40 (s, 3H), 2.51 (s, 3H), 3.00-3.18 (m, 1H), 3.31 (t, 1H, $J = 7.8$ Hz), 3.40-3.55 (m, 1H), 3.62 (br s, 1H), 6.80 (d, 2H, $J = 8.1$ Hz), 6.84-6.98 (m, 4H), 7.00-7.18 (m, 3H), 7.29 (d, 2H, $J = 8.1$ Hz), 7.56 (d, 2H, $J = 8.1$ Hz).

5

Example 13. (1*R*,5*S*)-2β-Phenyl-3α-(*p*-fluorophenyl)tropane (38).

Using a procedure similar to that described in Example 12, except replacing the compound 34 used therein with compound 35, the title compound 38 was prepared as a colorless oil: $[\alpha]^{25}_D -104^\circ$ (c 0.4, CHCl₃); ¹H NMR (CDCl₃)

10 δ 1.30 (t, 1H, $J = 13.2$ Hz), 1.50-1.75 (m, 2H), 2.10-2.56 (m, 4H), 2.23 (s, 3H), 2.32 (s, 3H), 2.99 (dt, 1H, $J = 7.5$ and 11.7 Hz), 3.28 (d, 1H, $J = 6.6$), 6.80 (t, 2H, $J = 8.7$ Hz), 6.89 (dd, 2H, $J = 5.7$ and 8.4 Hz), 7.00-7.20 (m, 5H).

The intermediate compound 35 was prepared as follows.

a. **1-Methyl-4-(*p*-fluorophenyl)-3-pyridiniumolate (27).** Using a procedure similar to that described by Kozikowski and co-worker, *J. Org. Chem.* 1997, 62, 503-509, compound 27 was prepared; mp 172°C (dec); ¹H NMR (CDCl₃) δ 3.97 (s, 3 H), 7.03-7.20 (m, 3 H), 7.34 (d, 1 H, $J = 6.3$ Hz), 7.54 (s, 1 H), 7.90-8.00 (m, 2H).

b. **N-Methyl (1*S*,5*S*,6*R*,*R*₂)-3-(*p*-fluorophenyl)-6-(*p*-tolylsulphinyl)-8-azabicyclo[3.2.1]oct-3-en-2-one (30).** A solution of 1-methyl-4-(*p*-fluorophenyl)-3-pyridiniumolate 27 (2.45 g, 12.04 mmol) and (+)-(R)-*p*-tolyl vinyl sulphoxide (2.00 g, 12.04 mmol) in dioxane (25 mL) was allowed to reflux for 20 hours. The resulting reaction mixture was concentrated under reduced pressure, purified by silica gel flash chromatography, and recrystallized from EtOAc to give the compound 30 as a white solid; $[\alpha]^{25}_D -77^\circ$ (c 1.25, CHCl₃); *R_f* 0.2 (EtOAc/hexane, 7/3); mp 186°C (EtOAc); ¹H NMR (CDCl₃) δ 1.64 (dd, $H_{7\alpha}$, $J = 8.7$ and 14.7 Hz), 2.14 (ddd, $H_{7\beta}$, $J = 3.6$, 7.8 and 14.7 Hz), 2.42 (s, 3H), 2.62 (s, 3H), 3.33 (dd, H_6 , $J = 3.6$ and 8.7 Hz), 3.73 (d, H_1 , $J = 7.5$ Hz), 4.51 (d, H_5 , $J = 5.4$ Hz), 7.01 (d, H_4 , $J = 5.4$ Hz), 7.041 (t, 2H, $J = 8.7$ Hz), 7.30-7.40 (m, 4H), 7.66 (d, 2H, $J = 8.1$ Hz).

c. **N-Methyl (1*S*,5*R*,7*R*,*R*₂)-4β-phenyl-3α-(*p*-fluorophenyl)-6β-(*p*-tolylsulphinyl)-8-azabicyclo[3.2.1]octan-2-one (32).** Using a procedure similar

to that described in Example 12, sub-part c, except replacing the compound 29 used therein with compound 30, the compound 32 was prepared as colorless oil; $[\alpha]_D^{25} +203^\circ$ (c 1.5, CHCl_3); $^1\text{H NMR}$ (CDCl_3) δ 2.03 (dd, 1H, $J = 8.7$ and 11.7 Hz), 2.25 (dd, 1H, $J = 6.9$ and 8.1 Hz), 2.31 (d, 1H, $J = 9.0$ Hz), 2.40 (s, 3H), 2.57 (s, 3H), 3.09 (t, 1H, $J = 8.4$ Hz), 3.74 (d, 1H, $J = 5.7$ Hz), 3.85 (s, 1H), 4.14 (d, 1H, $J = 9.0$ Hz), 6.73 (dd, 2H, $J = 5.4$ and 8.4 Hz), 6.86 (t, 2H, $J = 8.7$ Hz), 6.98-7.08 (m, 2H), 7.12-7.20 (m, 3H), 7.30 (d, 2H, $J = 8.1$ Hz), 7.55 (d, $J = 8.1$ Hz).

d. (1*S*,5*R*,7*R*,*R*_s)-2 β -phenyl-3 α -(*p*-fluorophenyl)-6 β -(*p*-tolylsulphynil) tropane (35). Using a procedure similar to that described in Example 12, sub-part d, except replacing the compound 31 used therein with compound 32, the compound 35 was prepared as colorless oil; $[\alpha]_D^{25} +107^\circ$ (c 1.5, CHCl_3); R_f 0.45 (EtOAc/hexane, 1/1); $^1\text{H NMR}$ (CDCl_3) δ 1.12-1.40 (m, 2H), 1.60 (dd, 1H, $J = 8.7$ and 12.9 Hz), 2.04-2.20 (m, 1H), 2.30 (d, 1H, $J = 10.2$ Hz), 2.24-2.45 (m, 1H), 2.39 (s, 3H), 2.50 (s, 3H), 3.06 (ddd, 1H, $J = 6.9$, 10.5 , and 12.6 Hz), 3.28 (t, 1H, $J = 8.4$ Hz), 3.42-3.55 (m, 1H), 3.63 (br s, 1H), 6.73-6.94 (m, 6H), 7.02-7.16 (m, 3H), 7.27 (d, 2H, $J = 8.1$ Hz), 7.55 (d, 2H, $J = 8.1$ Hz).

Example 14. (1*R*,5*S*)-2 β -*n*-Propyl-3 α -(*p*-fluorophenyl)tropane (39). Using a procedure similar to that described in Example 12, except replacing the compound 34 used therein with compound 36, the title compound 39 was prepared as colorless oil: $[\alpha]_D^{25} -40^\circ$ (c 0.3, CHCl_3); $^1\text{H NMR}$ (CDCl_3) δ 0.77 (t, 3H, $J = 7.2$ Hz), 1.00-1.56 (m, 8H), 2.02-2.26 (m, 2H), 2.23 (s, 3H), 2.30-2.44 (m, 1H), 2.44-2.60 (m, 1H), 2.94 (d, 1H, $J = 5.1$), 3.21 (t, 1H, $J = 6.3$ Hz), 6.94 (t, 2H, $J = 9.0$ Hz), 7.06-7.20 (m, 2H).

The intermediate compound 36 was prepared as follows.

a. *N*-Methyl (1*S*,5*R*,7*R*,*R*_s)-4 β -*n*-propyl-3 α -(*p*-fluorophenyl)-6 β -(*p*-tolylsulphynyl)-8-azabicyclo[3.2.1]octan-2-one (33). Using a procedure similar to that described in Example 12, sub-part c, except replacing the compound 29 used therein with compound 30 and replacing the phenyl magnesium bromide with propyl magnesium bromide, the compound 33 was prepared as a pale

yellow oil: $[\alpha]_D^{25} -71^\circ$ (c 0.5, CHCl_3); $^1\text{H NMR}$ (CDCl_3) δ 0.66 (t, 3H, $J = 7.2$ Hz), 0.70-0.90 (m, 1H), 1.10-1.36 (m, 3H), 1.40-1.55 (m, 1H), 1.98 (dd, 1H, $J = 8.7$ and 11.7 Hz), 2.20-2.35 (m, 1H), 2.42 (s, 3H), 2.53 (s, 3H), 2.92 (t, 1H, $J = 8.4$ Hz), 3.54 (d, 1H, $J = 8.4$ Hz), 3.61 (d, 1H, $J = 6.6$ Hz), 3.64 (s, 1H), 6.89 (dd, 2H, $J = 5.4$ and 8.4 Hz), 7.00 (t, 2H, $J = 8.7$ Hz), 7.34 (d, 2H, $J = 8.1$ Hz), 7.56 (d, $J = 8.1$ Hz).

b. **(1*S*,5*R*,7*R*,*R*₁)-2 β -*n*-Propyl-3 α -(*p*-fluorophenyl)-6 β -(*p*-tolylsulphynil)tropane (36).** Using a procedure similar to that described in Example 12, sub-part d, except replacing the compound 32 used therein with compound 33, the compound 36 was prepared as colorless oil; $[\alpha]_D^{25} +82^\circ$ (c 0.5, CHCl_3); R_f 0.3 (EtOAc/hexane, 1/1); $^1\text{H NMR}$ (CDCl_3) δ 0.62 (t, 3H, $J = 6.3$ Hz), 0.68-0.90 (m, 1H), 1.00-1.30 (m, 6H), 1.53 (dd, 1H, $J = 8.4$ and 12.6 Hz), 2.00-2.15 (m, 1H), 2.20-2.60 (m, 2H), 2.38 (s, 3H), 2.44 (s, 3H), 3.17 (t, 1H, $J = 8.1$ Hz), 3.28-3.42 (m, 1H), 3.39 (br s, 1H), 6.89 (t, 2H, $J = 8.7$ Hz), 7.03 (dd, 2H, $J = 5.7$ and 8.7 Hz), 7.30 (d, 2H, $J = 8.1$ Hz), 7.56 (d, 2H, $J = 8.1$ Hz); $^{13}\text{C NMR}$ (CDCl_3) δ 14.1, 19.4, 21.3, 32.0, 36.7, 39.4, 40.5, 41.3, 52.1, 60.5, 65.0, 72.5, 114.9 (d, $J_{\text{C-F}} = 85.2$ Hz), 124.3, 129.3 (d, $J_{\text{C-F}} = 30.6$ Hz), 129.9, 140.6 (d, $J_{\text{C-F}} = 11$ Hz), 141.2, 141.4, 161.2 (d, $J_{\text{C-F}} = 970$ Hz).

20 **Example 15. (1*R*,5*S*)-2 β -*n*-propyl-3 β -phenyltropane (21).**

Raney-Ni was added to a solution of 42 (70 mg, 0.19 mmol) in ethanol (4 mL) and the resulting mixture was refluxed for 2 h. Filtration through a pad of celite and concentration under reduced pressure afforded a mixture containing the two isomers 21 and 47 (ratio 75/25 at the GCMS analysis) which were separated by preparative thin layer chromatography on silica gel using EtOAc/hexane/ Et_3N (8/90/2) as eluent to afford the title compound 21 (6.0 mg, 13%) as a colorless oil: $[\alpha]_D^{25} -95^\circ$ (c 0.25, CH_2Cl_2).

The intermediate compound 42 was prepared as follows.

a. **1-Methyl-4-phenyl-3-hydroxypyridine (25).** A mixture of 2 (4.03 g, 12.9 mmol) and IRA-OH (400) resin (20 mL) in MeOH was stirred at 25 °C for 1 h then the basic resin was filtered off and washed several time with MeOH.

The resulting clear solution was concentrated under reduced pressure to afford the compound **3** (2.21 g, 92%) as a pale yellow solid used in the next step without further purification: mp 154-157 °C; ¹H NMR (DMSO-*d*₆) δ 3.97 (s, 3 H), 7.3-7.52 (m, 5 H), 7.38 (d, 1 H, *J* = 7.5 Hz), 8.04 (d, 1 H, *J* = 8.1 Hz), 8.053

5 (s, 1 H).

b. **N-Methyl (1*S*,5*S*,6*R*,*R*_s)-3-phenyl-6-(*p*-tolylsulphinyl)-8-azabicyclo[3.2.1]oct-3-en-2-one (28)**. To a solution of 1-methyl-4-phenyl-3-pyridiniumolate **25** (1.85 g, 10 mmol) in dioxane (50 mL) was added (+)-(R)-*p*-tolyl vinyl sulfoxide (1.61 g, 10 mmol). The resulting solution was refluxed
10 for 20 h, then concentrated under reduced pressure. dioxane at reflux for 20 h to give a mixture of both *exo* and *endo* cycloadducts (70:30). Silica gel flash column chromatography of the crude mixture leads to the separation of the 6-*exo* products (4:1 mixture of diastereoisomers; 55% overall yield) from the 6-*endo* product (one diastereoisomer, 22% yield). The major 6-*exo* diastereomer **28** was
15 obtained by crystallisation from EtOAc of the 4:1 mixture: [α]_D²⁵ -51° (c=0.5, acetone); *R*_f 0.6 (EtOAc); mp 166 °C (EtOAc); ¹H NMR (CDCl₃) δ 1.64 (dd, H_{7a}, *J* = 8.7 and 14.7 Hz), 2.14 (ddd, H_{7b}, *J* = 3.6, 7.5 and 14.7 Hz), 2.42 (s, 3H), 2.63 (s, 3H), 3.34 (dd, H₆, *J* = 3.3 and 8.7 Hz), 3.74 (d, H₁, *J* = 7.5 Hz), 4.51 (d, H₅, *J* = 5.4 Hz), 7.02 (d, H₄, *J* = 5.1 Hz), 7.3-7.4 (m, 7 H), 7.67 (d, 2H, *J* = 8.1
20 Hz); ¹³C NMR (CDCl₃) δ 21.5, 26.4, 34.7, 60.4, 69.3, 70.1, 125.4, 128.1, 128.3, 128.5, 130.2, 133.5, 138.6, 139.4, 141.3, 142.7, 197.0.

c. **N-Methyl (1*S*,5*S*,6*R*)-2-acetoxy-3-phenyl-6β-(*p*-tolylsulphenyl)-8-azabicyclo[3.2.1]oct-3-ene (40)**. Enone **28** (600 mg, 1.71 mmol) was dissolved in a solution of CeCl₃•7H₂O (700 mg, 1.88 mmol) in MeOH (10 mL), then
25 NaBH₄ (71 mg, 1.88 mmol) was added portionwise. This mixture was stirred at RT for 15 min, then concentrated under reduced pressure, diluted with water (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic phase was washed with brine (50 mL), dried and concentrated under reduced pressure to afford the allylic alcohol intermediate (620 mg).

30 To a solution of the crude alcohols (620 mg) in pyridine (6 mL) was added Ac₂O (2 mL). The resulting solution was stirred at RT for 15 h, then concentrated under reduced pressure, diluted with EtOAc (50 mL), and washed

with NH_4Cl (2 x 40 mL). Drying and concentration under reduced pressure afforded a crude mixture of the allylic acetates (660 mg, 97%) that was used in the next step without purification.

- Phosphorous trichloride (0.85 mL, 9.71 mmol) was added to a solution of the sulfoxide intermediate (660 mg) in dry DMF (15 mL) at 0 °C. After being stirred at 0 °C for 1 h, the reaction was quenched with a saturated solution of NaHCO_3 (60 mL) and extracted with ether (2 x 50 mL). The collected organic phase was washed with water (50 mL), brine (50 mL), dried and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel using EtOAc/hexane as eluent to afford the compound **40** (570 mg, 88%) as a mixture 3/1 of two isomers. R_f 0.7 (EtOAc/hexane 3/7). Major isomer: ^1H NMR (CDCl_3) δ 1.91 (s, 3H), 2.34 (s, 3H), 2.72 (s, 3H), 6.23 (d, 1H, $J = 5.1$ Hz), 6.33 (d, 1H, $J = 4.8$ Hz); Minor isomer ^1H NMR (CDCl_3) δ 1.94 (s, 3H), 2.32 (s, 3H), 2.61 (s, 3H), 5.39 (s, 1H), 6.37 (d, 1H, $J = 5.7$ Hz).
- d. **N-Methyl (1S,5S,7R)-3-phenyl-2 β -n-propyl-6 β -(p-tolylsulphenyl)-8-azabicyclo[3.2.1]oct-3-ene (42).** To a suspension of CuCN (27 mg, 0.3 mmol) in dry ether (2 mL) at -7 °C was added *n*-PrMgBr (3.0 mL, 1.0 M in ether). After 10 min, a solution of **40** (570 mg, 1.5 mmol) in dry ether (5 mL) was added dropwise. The resulting mixture was stirred at RT for 1.5 h and then diluted with ether (20 mL). The organic phase was washed with a saturated solution of NH_4Cl (2 x 20 mL), dried, and concentrated under reduced pressure. The crude mixture was purified by flash chromatography on silica gel using EtOAc/hexane as eluent to afford the compound **42** (420 mg, 77%) as a colorless oil: $[\alpha]_D^{25} +70^\circ$ (c 1.5, acetone); R_f 0.7 (EtOAc/hexane 3/7); ^1H NMR (CDCl_3) δ 0.78 (t, 3 H, $J = 7.2$ Hz), 1.1-1.6 (m, 4 H), 2.2-2.3 (m, 1H), 2.34 (s, 3H), 2.4-2.5 (m, 2H), 2.63 (s, 3H), 3.37 (br s, 1H), 3.51 (t, 1H, $J = 7.8$ Hz), 3.60 (t, 1H, $J = 5.1$ Hz), 6.10 (d, 1H, $J = 5.4$ Hz), 7.13 (d, 2H, $J = 8.1$ Hz), 7.2-7.3 (m, 7H); ^{13}C NMR (CDCl_3) δ 13.9, 21.0, 21.1, 34.3, 40.0, 42.1, 47.1, 49.7, 62.3, 70.5, 126.0, 127.1, 128.3, 129.6, 129.7, 130.0, 134.0, 136.2, 138.4, 140.2.

Example 16. (1R,5S)-2 β -n-propyl-3 α -phenyltropane (47).

The title compound was isolated from the chromatography of Example

15 as a colorless oil: $[\alpha]^{25}_D -50^\circ$ (c 1.0, CH_2Cl_2); ^1H NMR (CDCl_3) δ 0.77 (t, 3H, $J = 7.5$ Hz), 1.0-1.6 (m, 8H), 2.0-2.3 (m, 2H), 2.23 (s, 3H), 2.32-2.6 (m, 2H), 2.95 (d, 1H, $J = 6.0$ Hz), 3.21 (bt, 1H, $J = 7.5$ Hz), 7.1-7.35 (m, 5H); ^{13}C NMR (CDCl_3) δ 14.2, 19., 29.0, 29.5, 37.0, 40.6, 41.6, 41.8, 50.6, 59.5, 65.0, 125.7, 128.1, 128.2, 146.2; MS m/z (%) 243 (M^+ , 5), 214 (3), 96 (42), 83 (100).

Example 17. (1R,5S)-2 β -Phenyl-3 β -phenyltropane (48).

Using a procedure similar to that described in Example 15, except replacing the compound 42 used therein with compound 43, compounds 48 and 49 were prepared and separated by chromatography to give the title compound as a colorless oil: $[\alpha]^{25}_D -76^\circ$ (c 1.0, CH_2Cl_2); ^1H NMR (CDCl_3) δ 1.64 (dt, 1H, $J = 4.2$ and 13.5 Hz), 1.72-1.86 (m, 2H), 2.06-2.30 (m, 2H), 2.25 (s, 3H), 2.39 (dt, 1H, $J = 2.4$ and 12.9 Hz), 2.84-2.92 (m, 1H), 3.26-3.42 (m, 3H), 6.85 (d, 2H, $J = 8.1$ Hz), 6.95-7.12 (m, 5H), 7.35-7.45 (m, 2H); ^{13}C NMR (CDCl_3) δ 25.1, 27.3, 35.2, 37.5, 42.0, 53.3, 61.9, 67.7, 125.4, 125.5, 127.0, 127.5, 128.0, 130.6, 142.8, 143.2.

The intermediate compound 43 was prepared as follows.

a. **N-Methyl (1S,5S,7R)-2,3-(di-phenyl)-6 β -(*p*-tolylsulphenyl)-8-azabicyclo[3.2.1]oct-3-ene (43).** Using a procedure similar to that described in Example 15, sub-part d, except replacing the *n*-PrMgBr used therein with PhMgBr, the compound 43 was prepared as a colorless oil: ^1H NMR (CDCl_3) δ 2.3-2.4 (m, 1H), 2.37 (s, 3H), 2.43 (s, 3H), 2.52 (dd, 1H, $J = 8.1$ and 12.3 Hz), 3.40 (s, 1H), 3.67 (t, 1H, $J = 7.5$ Hz), 3.75 (br s, 1H), 6.51 (d, 1H, $J = 5.7$ Hz), 7.0-7.5 (m, 14H).

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Example 18. (1R,5S)-2 β -Phenyl-3 α -phenyltropane (49).

The title compound was isolated from the chromatography of Example 17 as a colorless oil; $[\alpha]^{25}_D -55^\circ$ (c 0.2, CH_2Cl_2); ^1H NMR (CDCl_3) δ 1.38 (t, 1H, $J = 13.2$, 1.54-1.80 (m, 2H), 2.16-2.40 (m, 2H), 2.35 (s, 3H), 2.44-2.60 (m, 2H), 2.96-3.10 (m, 1H), 3.32 (d, 1H, $J = 6.3$ Hz), 3.36-3.46 (m, 1H), 6.98 (d, 2H, $J = 8.1$ Hz), 7.00-7.20 (m, 8H); ^{13}C NMR (CDCl_3) δ 29.7, 29.8, 40.9, 41.3, 43.6, 58.7, 59.5, 68.1, 125.7, 125.8, 127.3, 127.9, 128.0, 128.3, 144.6, 147.5.

Example 19. N-Methyl (1S,5S,7R)-2 β -phenyl-3-(p-tolyl)tropane (50).

Using a procedure similar to that described in Example 15, except replacing the compound 42 used therein with compound 46, the title compound 50 was prepared as a colorless oil: $[\alpha]_D^{25} -160^\circ$ (c 0.2, CH₂Cl₂); ¹H NMR (CDCl₃) δ 1.62 (dt, 1H, *J* = 4.2 and 13.5 Hz), 1.72-1.86 (m, 2H), 2.04-2.30 (m, 2H), 2.17 (s, 3H), 2.23 (s, 3H), 2.36 (dt, 1H, *J* = 2.4 and 12.9 Hz), 2.84-2.92 (m, 1H), 3.24-3.42 (m, 3H), 6.74 (d, 2H, *J* = 8.1 Hz), 6.85 (d, 2H, *J* = 8.1 Hz), 7.00-7.15 (m, 3H), 7.37-7.45 (m, 2H); ¹³C NMR (CDCl₃) δ 20.9, 25.1, 27.3, 35.5, 37.0, 42.0, 53.2, 62.0, 67.8, 125.4, 127.0, 127.8, 128.2, 130.7, 134.8, 140.1, 143.0; MS *m/z* (%) 291 (M⁺, 8), 178 (4), 96 (60), 82 (100).

The intermediate compound 46 was prepared as follows.

a. **N-Methyl (1S,5S,6R)-2-acetoxy-3-(p-tolyl)-6 β -(p-tolylsulphenyl)-8-azabicyclo[3.2.1]oct-3-ene (41).** Using a procedure similar to that described in Example 15, sub-part c, except replacing the compound 28 used therein with compound 29, the compound 41 was prepared as a mixture 3/1 of two isomers. *R_f* 0.7 (EtOAc/hexane 3/7). Major isomer (α -acetoxy derivatives): ¹H NMR (CDCl₃) δ 1.92 (s, 3H), 2.34 (s, 3H), 1.90-2.06 (m, 1H), 2.33 (s, 3H), 2.34 (s, 3H), 2.72 (s, 3H), 2.65-2.80 (m, 1H), 3.43 (d, 1H, *J* = 5.1 Hz), 3.65-3.84 (m, 2H), 6.20 (d, 1H, *J* = 5.1 Hz), 6.32 (d, 1H, *J* = 4.5 Hz), 7.05-7.20 (m, 6H), 7.31 (d, 2H, *J* = 7.8 Hz); Minor isomer (β -acetoxy derivatives): ¹H NMR (CDCl₃) δ 1.96 (s, 3H), 2.10-2.25 (m, 1H), 2.33 (s, 3H), 2.34 (s, 3H), 2.60 (s, 3H), 3.50-65 (m, 3H), 5.38 (s, 1H), 6.33 (d, 1H, *J* = 5.4 Hz), 7.05-7.30 (m, 8H).

b. **N-Methyl (1S,5S,7R)-2 β -phenyl-3-(p-tolyl)-6 β -(p-tolylsulphenyl)-8-azabicyclo[3.2.1]oct-3-ene (46).** Using a procedure similar to that described in Example 15, sub-part d, except replacing the compound 40 used therein with compound 41, and replacing the n-PrMgBr used therein with PhMgBr, the compound 46 was prepared as a colorless oil; ¹H NMR (CDCl₃) δ 2.20-2.35 (m, 1H), 2.22 (s, 3H), 2.37 (s, 3H), 2.42 (s, 3H), 2.50 (dd, 1H, *J* = 8.4 and 12.6 Hz), 3.39 (s, 1H), 3.67 (t, 1H, *J* = 8.4 Hz), 3.66-3.78 (m, 2H), 6.48 (d, 1H, *J* = 5.4 Hz), 6.96 (d, 2H, *J* = 8.1 Hz), 7.00-7.30 (m, 9H), 7.36 (d, 2H, *J* = 8.1 Hz); ¹³C NMR (CDCl₃) δ 21.0, 21.1, 40.1, 41.7, 49.8, 52.9, 62.2, 75.6, 115.3, 120.2, 125.4, 125.8, 127.9, 128.1, 128.9, 129.8, 130.2, 130.5, 133.9, 134.0, 136.4,

136.7, 142.7.

Example 20. N-Methyl (1S,5S,7R)-2 β -n-propyl-3 β -(p-tolyl)tropane (51).

Using a procedure similar to that described in Example 15, except
5 replacing the compound 42 used therein with compound 44, the title compound
51 was prepared as a colorless oil: ^1H NMR (CDCl_3) δ 0.78 (t, 3H, $J = 7.2$ Hz),
1.08-1.56 (m, 8H), 2.04-2.24 (m, 2H), 2.23 (s, 3H), 2.30 (s, 3H), 2.28-2.58 (m,
2H), 2.94 (d, 1H, $J = 6.3$ Hz), 3.19 (t, 1H, $J = 7.8$ Hz), 7.06 (s, 4H); ^{13}C NMR
(CDCl_3) δ 14.2, 19.9, 21.0, 29.0, 29.5, 37.0, 40.1, 41.6, 41.9, 50.6, 59.6, 64.9,
10 128.1, 128.8, 135.1, 143.1.

The intermediate compound 44 was prepared as follows.

a. **N-Methyl (1S,5S,7R)-2 β -n-propyl-3-(p-tolyl)-6 β -(p-tolylsulphenyl)-8-azabicyclo[3.2.1]oct-3-ene (44).** Using a procedure similar to that described in
Example 15, sub-part d, except replacing the compound 40 used therein with
15 compound 41, the title compound 44 was prepared as a colorless oil: $[\alpha]_D^{25}$
+110° (c 2.6, CH_2Cl_2); R_f 0.5 (EtOAc/hexane, 1/4); ^1H NMR (CDCl_3) δ 0.81 (t,
3 H, $J = 7.2$ Hz), 1.2-1.6 (m, 4 H), 2.2-2.3 (m, 1H), 2.35 (s, 3H), 2.4-2.5 (m, 2H),
2.65 (s, 3H), 3.39 (br s, 1H), 3.53 (t, 1H, $J = 7.8$ Hz), 3.60 (t, 1H, $J = 5.4$ Hz),
6.08 (d, 1H, $J = 6.0$ Hz), 7.10-7.24 (m, 6H); 7.32 (d, 2H, $J = 8.1$ Hz), ^{13}C NMR
20 (CDCl_3) δ 14.0, 21.0, 21.1, 34.3, 40.0, 42.1, 47.1, 49.7, 62.3, 70.6, 125.8, 128.8,
129.0, 129.7, 129.9, 134.1, 136.1, 136.9, 137.3, 138.2.

Example 21. N-Methyl (1S,5S,7R)-2 β -n-butyl-3 α -(p-tolyl)tropane (52).

Using a procedure similar to that described in Example 15, except
25 replacing the compound 42 used therein with compound 45, the title compound
52 was prepared as a colorless oil: $[\alpha]_D^{25}$ -42° (c 0.5, CH_2Cl_2); ^1H NMR (CDCl_3)
 δ 0.80 (t, 3H, $J = 6.6$ Hz), 1.08-1.56 (m, 10H), 2.04-2.24 (m, 2H), 2.23 (s, 3H),
2.30 (s, 3H), 2.28-2.58 (m, 2H), 2.94 (d, 1H, $J = 6.0$ Hz), 3.19 (t, 1H, $J = 7.8$
Hz), 7.06 (s, 4H); ^{13}C NMR (CDCl_3) δ 14.1, 20.9, 22.8, 28.9, 29.0, 29.5, 34.3,
30 40.0, 41.6, 41.8, 50.8, 59.5, 64.9, 128.1, 128.8, 135.1, 143.1.

The intermediate compound 45 was prepared as follows.

a. **N-Methyl (1S,5S,7R)-2 β -n-butyl-3-(p-tolyl)-6 β -(p-tolylsulphenyl)-8-**

azabicyclo[3.2.1]oct-3-ene (45). Using a procedure similar to that described in Example 15, sub-part d, except replacing the compound 40 used therein with compound 41, and replacing the n-BuMgBr with n-PrMgBr, the compound 45 was prepared as a colorless oil: $[\alpha]_D^{25} +79^\circ$ (c 1.0, EtOH); ^1H NMR (CDCl_3) δ 0.80 (t, 3H, $J = 6.6$ Hz), 1.00-1.40 (m, 5H), 1.40-1.60 (m, 1H), 2.20-2.50 (m, 3H), 2.32 (s, 3H), 2.33 (s, 3H), 2.63 (s, 3H), 3.35 (s, 1H), 3.50 (t, 1H, $J = 7.2$ Hz), 3.58 (t, 1H, $J = 5.1$ Hz), 6.06 (d, 1H, $J = 5.4$ Hz), 7.00-7.20 (m, 6H), 7.31 (d, 2H, $J = 8.1$ Hz); ^{13}C NMR (CDCl_3) δ 14.0, 20.9, 21.0, 22.5, 30.3, 31.7, 39.9, 42.1, 47.3, 49.8, 62.3, 70.4, 125.8, 128.7, 129.0, 129.7, 130.2, 134.0, 136.2, 136.8, 137.2, 138.2.

Example 22. Synthesis of ethyl 8-Methyl-2-oxo-3-phenyl-8-azabicyclo[3.2.1]oct-3-ene-6-carboxylate and ethyl 8-methyl-2-oxo-3-phenyl-8-azabicyclo[3.2.1]oct-3-ene-7-carboxylate (6a-d). Using a procedure similar to that described in Example 7, except replacing the phenyl vinylsulfone used therein with methyl acrylate, compounds 6a-6d were prepared as a mixture of four isomers and separated by silica gel column chromatography using EtOAc/n-hexane as eluant. 6a (33%): dark yellow oil; $R_f = 0.70$ (EtOAc/n-hexane 1/1); ^1H NMR (CDCl_3) δ 1.312 (t, 3 H, $J = 6.9$ Hz), 1.99 (dd, $\text{H}_{7\text{endo}}$, $J_{7\text{en-6}} = 9.9$ Hz, $J_{7\text{en-7ex}} = 14.1$ Hz), 2.52 (s, 3 H), 2.90 (qd, $\text{H}_{7\text{exo}}$, $J_{7\text{ex-6}} = 3.6$ Hz, $J_{7\text{ex-7}} = 7.8$ Hz, $J_{7\text{ex-7en}} = 13.8$ Hz), 3.02 (dd, H_6 , $J_{6-7\text{ex}} = 3.6$ Hz, $J_{6-7\text{en}} = 9.0$ Hz), 3.74 (d, H_5 , $J_{5-4} = 7.5$ Hz), 4.23 (q, 2 H, $J = 7.2$ Hz), 7.07 (d, H_4 , $J_{4-5} = 5.4$ Hz), 7.3-7.4 (m, 5 H); ^{13}C NMR (CDCl_3) δ 14.20, 27.84, 35.83, 47.52, 61.44, 63.61, 70.72, 128.23, 128.28, 133.95, 137.93, 143.61, 172.83, 197.86. 6b (26%): yellow oil; $R_f = 0.4$ (EtOAc/n-hexane 1/1); ^1H NMR (CDCl_3) δ 1.25 (t, 3 H, $J = 7.2$ Hz), 2.11 (dd, $\text{H}_{7\text{endo}}$, $J_{7\text{en-6}} = 6.0$ Hz, $J_{7\text{en-7ex}} = 14.4$ Hz), 2.48 (s, 3 H), 2.64 (qd, $\text{H}_{7\text{exo}}$, $J_{7\text{ex-6}} = 7.8$ Hz, $J_{7\text{ex-7}} = 10.2$ Hz, $J_{7\text{ex-7en}} = 13.8$ Hz), 3.60 (dt, H_6 , $J_{6-5} = J_{6-7\text{en}} = 5.7$ Hz, $J_{6-7\text{ex}} = 10.5$ Hz), 3.70 (d, H_1 , $J_{1-7\text{ex}} = 8.1$ Hz), 4.20 (t, H_5 , $J_{5-4} = J_{5-6} = 5.4$ Hz), 6.98 (d, H_4 , $J_{4-5} = 5.1$ Hz), 7.34 (bs, 5 H). 6c (20%): pale yellow oil; $R_f = 0.6$ (EtOAc/n-hexane 1/1); ^1H NMR (CDCl_3) δ 1.30 (t, 3 H, $J = 7.2$ Hz), 2.22 (dd, $\text{H}_{6\text{endo}}$, $J_{6\text{en-7}} = 9.6$ Hz, $J_{6\text{en-6ex}} = 12.6$ Hz), 2.795 (dt, $\text{H}_{6\text{exo}}$, $J_{6\text{ex-5}} = J_{6\text{ex-7}} = 6.3$ Hz, $J_{6\text{ex-6en}} = 12.6$ Hz), 3.534 (dd, H_7 , $J_{7-6\text{ex}} = 6.6$ Hz, $J_{7-6\text{en}} = 9.3$ Hz), 3.97 (t, H_5 , $J_{5-4} = J_{5-6} = 5.7$

- Hz), 4.01 (s, H₁), 7.08 (d, H₄, $J_{4,5} = 5.4$ Hz), 7.36 (bs, 5 H); ¹³C NMR (CDCl₃) δ 14.18, 32.45, 37.10, 43.39, 61.49, 61.65, 74.17, 128.20, 128.26, 129.87, 132.90, 134.03, 136.83, 146.61, 173.43, 195.92. 6d (12%): pale yellow oil; $R_f = 0.35$ (EtOAc/*n*-hexane 1/1); ¹H NMR (CDCl₃) δ 1.20 (t, 3 H, $J = 7.2$ Hz), 2.30 (dd, H_{6endo}, $J_{6en-7} = 3.9$ Hz, $J_{6en-6ex} = 12.3$ Hz), 2.47 (s, 3 H), 2.52 (qd, H_{6exo}, $J_{6ex-5} = 6.6$ Hz, $J_{6ex-7} = 10.5$ Hz, $J_{6ex-6en} = 12.4$ Hz), 3.64 (m, H₇), 3.87 (t, H₅, $J_{5,4} = J_{5-6ex} = 6.0$ Hz), 3.95 (d, H₁, $J_{1,7} = 7.2$ Hz), 4.07 (q, 2 H, $J = 7.2$ Hz), 7.11 (d, H₄, $J_{4,5} = 5.7$ Hz), 7.33 (bs, 5 H).

- Example 26.** The following illustrate representative pharmaceutical dosage forms, containing a compound of formula I ('Compound X'), for therapeutic or prophylactic use in mammals such as humans.

		<u>mg/tablet</u>
(i) <u>Tablet 1</u>		
	'Compound X'	100.0
	Lactose	77.5
15	Povidone	15.0
	Croscarmellose sodium	12.0
	Microcrystalline cellulose	92.5
	Magnesium stearate	<u>3.0</u>
		300.0
(ii) <u>Tablet 2</u>		<u>mg/tablet</u>
	'Compound X'	20.0
	Microcrystalline cellulose	410.0
	Starch	50.0
25	Sodium starch glycolate	15.0
	Magnesium stearate	<u>5.0</u>
		500.0
(iii) <u>Capsule</u>		<u>mg/capsule</u>
30	'Compound X'	10.0
	Colloidal silicon dioxide	1.5
	Lactose	465.5
	Pregelatinized starch	120.0
	Magnesium stearate	<u>3.0</u>
35		600.0
(iv) <u>Injection 1 (1 mg/ml)</u>		<u>mg/ml</u>
	'Compound X' (free acid form)	1.0
	Dibasic sodium phosphate	12.0
40	Monobasic sodium phosphate	0.7
	Sodium chloride	4.5
	1.0 N Sodium hydroxide solution	

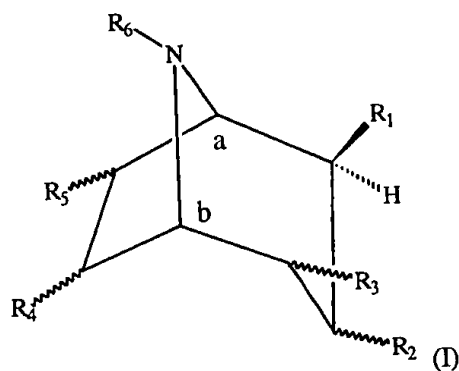
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- | | | |
|----|---|---------------|
| | (pH adjustment to 7.0-7.5) | q.s. |
| | Water for injection | q.s. ad 1 mL |
| | <u>(v) Injection 2 (10 mg/ml)</u> | <u>mg/ml</u> |
| 5 | 'Compound X' (free acid form) | 10.0 |
| | Monobasic sodium phosphate | 0.3 |
| | Dibasic sodium phosphate | 1.1 |
| | Polyethylene glycol 400 | 200.0 |
| | 01 N Sodium hydroxide solution | |
| 10 | (pH adjustment to 7.0-7.5) | q.s. |
| | Water for injection | q.s. ad 1 mL |
| | <u>(vi) Aerosol</u> | <u>mg/can</u> |
| | 'Compound X' | 20.0 |
| 15 | Oleic acid | 10.0 |
| | Trichloromonofluoromethane | 5,000.0 |
| | Dichlorodifluoromethane | 10,000.0 |
| | Dichlorotetrafluoroethane | 5,000.0 |
| 20 | The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. | |

- The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that
- 25 many variations and modifications may be made while remaining within the spirit and scope of the invention.

WHAT IS CLAIMED IS:

1. A compound of formula (I):



wherein

R_1 is hydrogen, aryl, aryl(C_1 - C_4)alkyl, (C_1 - C_4)alkyl, OR_7 , or $N(R_8)_2$;

R_2 is aryl or aryl(C_1 - C_4)alkyl;

R_3 is hydrogen, (C_1 - C_4)alkyl, (C_2 - C_4)alkenyl or (C_2 - C_4)alkynyl;

R_4 and R_5 are independently hydrogen, halo, CN, OR_9 , $COOR_{10}$,

aryl SO_2 -, or $-CH_2NHR_{11}$;

R_6 is hydrogen, (C_1 - C_4)alkyl, (C_1 - C_4)alkenyl, (C_1 - C_4)alkynyl, aryl, or

aryl(C_1 - C_4)alkyl;

R_7 is hydrogen, (C_1 - C_4)alkyl, (C_1 - C_5)alkanoyl, arylcarbonyl, or aryl (C_1 -

C_5)alkanoyl;

each R_8 is independently hydrogen, (C_1 - C_4)alkyl, (C_1 - C_4)alkanoyl, aryl, aryl(C_1 - C_4)alkyl, or arylcarbonyl;

R_9 is hydrogen, (C_1 - C_4)alkyl, (C_1 - C_5)alkanoyl, or arylcarbonyl;

R_{10} is hydrogen or (C_1 - C_4)alkyl; and

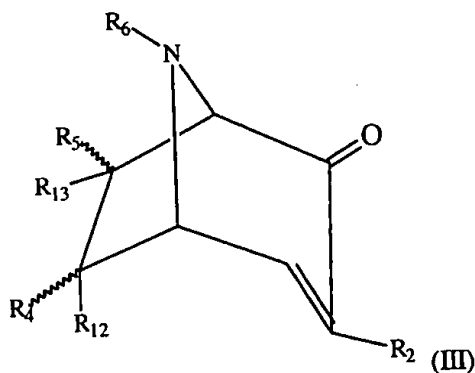
R_{11} is hydrogen or (C_1 - C_4)alkyl;

wherein any aryl in R_1 , R_2 , and R_6 - R_9 may optionally be substituted with

- 1, 2, or 3 substituents independently selected from the group consisting of halo (preferably I or Cl), CF_3 , $(\text{C}_1\text{-C}_4)\text{alkoxy}$, $(\text{C}_1\text{-C}_4)\text{alkyl}$, $(\text{C}_1\text{-C}_4)\text{alkenyl}$, $(\text{C}_1\text{-C}_4)\text{alkynyl}$, amino, nitro cyano, and aryl;
or a pharmaceutically acceptable salt thereof.
2. The compound of claim 1 wherein R_1 is OR_7 .
3. The compound of claim 1 wherein R_1 is hydrogen, aryl, $(\text{C}_1\text{-C}_4)\text{alkyl}$, OR_7 , or $\text{N}(\text{R}_8)_2$; wherein any aryl in R_1 may optionally be substituted with 1, 2, or 3 substituents independently selected from the group consisting of halo (preferably I or Cl), CF_3 , $(\text{C}_1\text{-C}_4)\text{alkoxy}$, $(\text{C}_1\text{-C}_4)\text{alkyl}$, $(\text{C}_1\text{-C}_4)\text{alkenyl}$, $(\text{C}_1\text{-C}_4)\text{alkynyl}$, amino, nitro and cyano.
4. The compound of claim 1 wherein R_1 is hydrogen, OR_7 , or $\text{N}(\text{R}_8)_2$.
5. The compound of claim 1 wherein R_1 is aryl, $\text{aryl}(\text{C}_1\text{-C}_4)\text{alkyl}$, OR_7 , or $\text{N}(\text{R}_8)_2$.
6. The compound of claim 1 wherein R_1 is OR_7 , or $\text{N}(\text{R}_8)_2$.
7. The compound of claim 1 wherein R_2 is aryl or $\text{aryl}(\text{C}_1\text{-C}_4)\text{alkyl}$; wherein the aryl is substituted with 1, 2, or 3 substituents independently selected from the group consisting of halo (preferably I or Cl), CF_3 , $(\text{C}_1\text{-C}_4)\text{alkoxy}$, $(\text{C}_1\text{-C}_4)\text{alkenyl}$, $(\text{C}_1\text{-C}_4)\text{alkynyl}$, amino, nitro and cyano.
8. The compound of claim 1 wherein R_3 is $(\text{C}_2\text{-C}_4)\text{alkenyl}$ or $(\text{C}_2\text{-C}_4)\text{alkynyl}$.
9. The compound of claim 1 wherein R_3 is $(\text{C}_1\text{-C}_4)\text{alkyl}$, $(\text{C}_2\text{-C}_4)\text{alkenyl}$ or $(\text{C}_2\text{-C}_4)\text{alkynyl}$.
10. The compound of claim 5 wherein R_3 is $(\text{C}_1\text{-C}_4)\text{alkyl}$, $(\text{C}_2\text{-C}_4)\text{alkenyl}$ or

(C₂-C₄)alkynyl.

11. The compound of claim 5 wherein R₃ is (C₁-C₄)alkyl or (C₂-C₄)alkynyl.
12. The compound of claim 1 wherein R₇ is (C₁-C₅)alkanoyl, arylcarbonyl, or aryl (C₁-C₃)alkanoyl.
13. The compound of claim 1 wherein one of R₄ and R₅ is hydrogen, and the other is halo, CN, OR₉, COOR₁₀, arylSO₂⁻, or -CH₂NHR₁₁.
14. The compound of any one of claims 1-13 wherein the carbon designated "a" has the (R) stereochemistry and the carbon designated "b" has the (S) stereochemistry.
15. The compound (1*R*,5*S*)-2β-phenyl-3α-phenyltropane; or a pharmaceutically acceptable salt thereof.
16. A pharmaceutical composition comprising an effective amount of a compound of claim 1, in combination with a pharmaceutically acceptable diluent or carrier.
17. A method of synthesizing a compound of formula (III):



wherein

R_2 is aryl or aryl(C_1 - C_4)alkyl;

R_4 and R_5 are independently hydrogen, halo, CN, OR_9 , $COOR_{10}$,

$-CH_2NHR_{11}$, or a chiral oxillary;

R_6 is hydrogen, (C_1 - C_4)alkyl, (C_1 - C_4)alkenyl, (C_1 - C_4)alkynyl, aryl, or aryl(C_1 - C_4)alkyl;

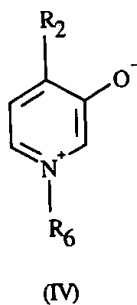
R_9 is hydrogen, (C_1 - C_4)alkyl, (C_1 - C_5)alkanoyl, or arylcarbonyl;

R_{10} is hydrogen or (C_1 - C_4)alkyl;

R_{11} is hydrogen or (C_1 - C_4)alkyl; and

R_{12} and R_{13} are each hydrogen; or one of R_{12} and R_{13} is hydrogen, and the other is a chiral auxiliary (such as for example a (+)-(R)-p-tolylsulfinyl, or a (-)-(S)-p-tolylsulfinyl substituent).

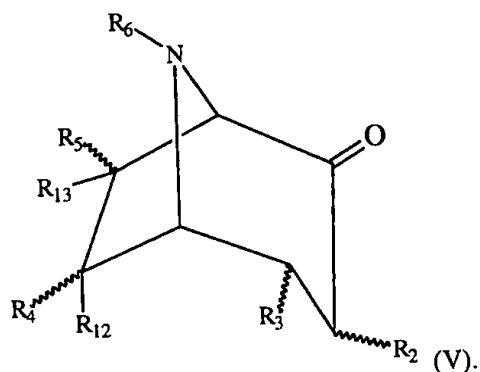
wherein any aryl in R_2 , R_6 and R_9 may optionally be substituted with 1, 2, or 3 substituents independently selected from the group consisting of halo (preferably I or Cl), CF_3 , (C_1 - C_4)alkoxy, (C_1 - C_4)alkyl, (C_2 - C_4)alkenyl, (C_2 - C_4)alkynyl, amino, nitro cyano, or aryl; comprising reacting a compound of formula (IV):



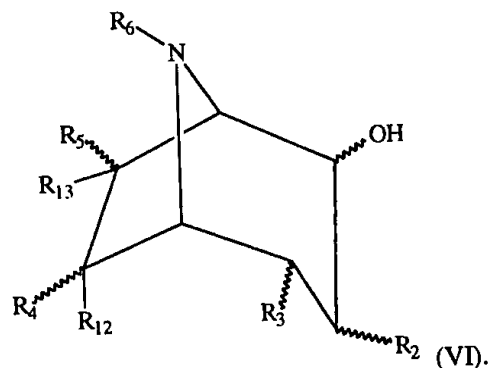
with $(R_4)(R_{12})C=C(R_5)(R_{13})$.

18. The method of claim 17 further comprising reacting the compound of formula (III) with R_3-MgBr , where R_3 is (C_1 - C_4)alkyl, (C_2 - C_4)alkenyl or (C_2 - C_4)alkynyl; a source of Cu(I), and a hydroxy protecting reagent such as ((C_1 -

C_4 alkyl) $_3$ SiCl followed by removal of the protecting group, to yield a compound of formula (V):



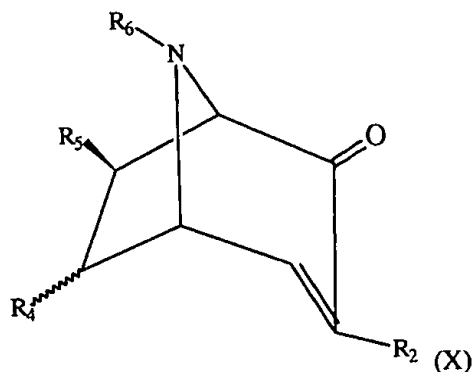
19. The method of claim, 18 further comprising reducing the keto group in the compound of formula (V) to yield a compound of formula (VI):



and reacting the compound of formula (VI) with an anhydride of the formula $CH_3C(O)O-R_7$, where R_7 is (C_1-C_5) alkanoyl, arylcarbonyl, or aryl (C_1-C_5) alkanoyl to yield a compound of formula (I) wherein R_1 is OR_7 .

20. The method of claim 17, 18, or 19, wherein one of R_{12} and R_{13} is hydrogen and the other is a chiral auxiliary, further comprising removing the chiral auxiliary to give a corresponding compound of formula III, IV, or V wherein R_{12} and R_{13} are each hydrogen.

21. A method of synthesizing a compound of formula (X):



wherein

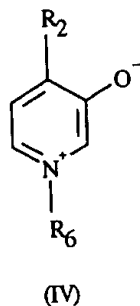
R_2 is aryl or aryl(C_1 - C_4)alkyl;

R_4 and R_5 are hydrogen or arylSO₂-, provided that one of R_4 or R_5 is H and the other is arylSO₂-; and

R_6 is hydrogen, (C_1 - C_4)alkyl, (C_2 - C_4)alkenyl, (C_2 - C_4)alkynyl, aryl, or aryl(C_1 - C_4)alkyl;

wherein any aryl in R_2 or R_6 may optionally be substituted with 1, 2, or 3 substituents independently selected from the group consisting of halo (preferably I or Cl), CF₃, (C_1 - C_4)alkoxy, (C_1 - C_4)alkyl, (C_2 - C_4)alkenyl, (C_2 - C_4)alkynyl, amino, nitro cyano, and aryl;

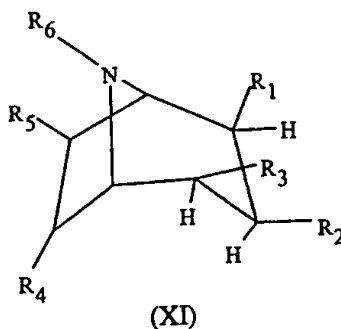
comprising reacting a compound of formula (IV):



with CH₂=CH-SO₂aryl.

22. A method for the treatment of drug addiction comprising administering to a human in need of such treatment, a pharmaceutically effective dose of at least one compound of formula I; or a pharmaceutically acceptable salt thereof.
23. A therapeutic method comprising inducing analgesia or vasoconstriction in a mammal, by administering an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof.
24. A therapeutic method for treating a disease or condition in which the activity of dopamine or serotonin has been implicated and modulation of dopamine or serotonin uptake is desired comprising administering to a mammal in need of such treatment, a pharmaceutically effective dose of at least one compound of formula I; or a pharmaceutically acceptable salt thereof.
25. A therapeutic method for treating a disease or condition in which the activity of dopamine has been implicated and modulation of dopamine uptake is desired comprising administering to a mammal in need of such treatment, a pharmaceutically effective dose of at least one compound of formula I; or a pharmaceutically acceptable salt thereof.
26. The method of claim 25 wherein the disease or condition is depression, obesity or Parkinson's disease.
27. A method of imaging the brain of a mammal (i.e. a human) comprising administering to said mammal, a detectable amount of a radiolabeled compound, comprising a radionuclide bound to a compound of formula (I), or a pharmaceutically acceptable salt thereof; and subsequently detecting the presence of said radiolabeled compound.
28. A radiolabeled compound comprising a radionuclide bound to a compound of formula I; or a pharmaceutically acceptable salt thereof.

29. A compound of formula (XI):



wherein

R_1 is H, OR₇, where R_7 is H, (C₁-C₄)alkyl, (C₁-C₄)alkylC(O)-, (C₅-C₇)arylC(O)-; NHR₈ where R_8 is H, (C₁-C₄)alkyl, (C₁-C₄)alkyl(CO)- or (C₅-C₇)arylC(O)-;

R_2 is phenyl or benzyl, each optionally substituted with halo, CF₃, (C₁-C₄)alkoxy,

(C₁-C₄)alkyl, (C₁-C₄)alkenyl, (C₁-C₄)alkynyl, amino, nitro or (C₅-C₇)aryl;

R_3 is (C₁-C₄)alkyl, (C₁-C₄)alkenyl or (C₁-C₄)alkynyl;

R_4 and R_5 are independently H, halo, CN, OR₉, where R_9 is H, (C₁-C₄)alkyl, (C₁-C₄)alkylC(O)-, (C₅-C₇)arylC(O)-; COOR₁₀ where R_{10} is H or (C₁-C₄)alkyl; or CH₂NHR₁₁, where R_{11} is H or (C₁-C₄)alkyl; and

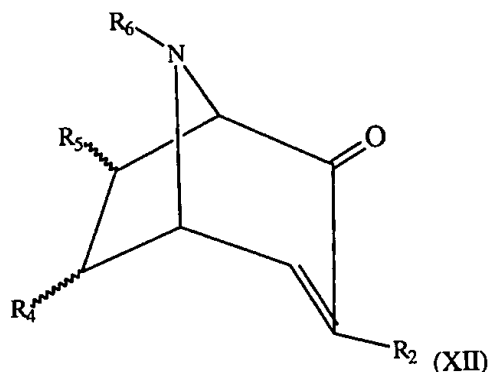
R_6 is H, (C₁-C₄)alkyl, (C₁-C₄)alkenyl, (C₁-C₄)alkynyl or benzyl; or a stereoisomer thereof; or a pharmaceutically acceptable salt thereof.

30. The compound of claim 29 wherein R_2 is phenyl.

31. The compound of claim 30 wherein the phenyl is substituted with I or Cl.

32. The compound of claim 29 wherein R_6 is (C₁-C₄)alkyl.

33. A method of synthesizing a compound of formula (XII):

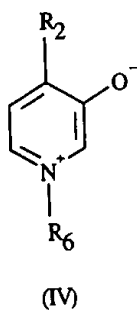


wherein

R_2 is phenyl or benzyl, each optionally substituted with halo, CF_3 , (C_1-C_4) alkoxy, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, amino, nitro or (C_5-C_7) aryl;

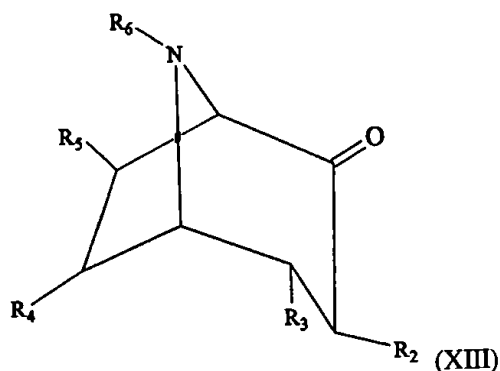
R_4 and R_5 are independently H, halo, CN, OR_9 where R_9 is H, (C_1-C_4) alkyl, (C_1-C_4) alkylC(O)-, (C_5-C_7) arylC(O)-; $COOR_{10}$ where R_{10} is H or (C_1-C_4) alkyl; or CH_2NHR_{11} , where R_{11} is H or (C_1-C_4) alkyl, provided that one of R_4 and R_5 is H; and

R_6 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl or benzyl;
comprising the steps of reacting a compound of formula (IV):

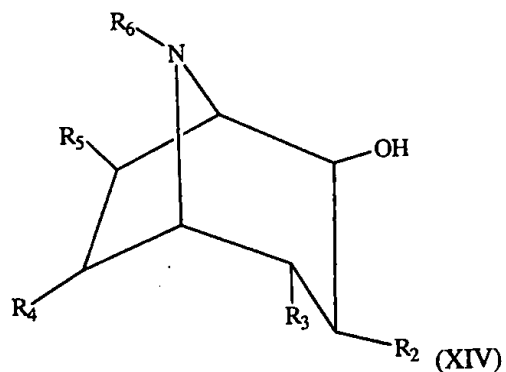


with $CH_2=CH-R$ where R is halo, CN, OR_9 , $COOR_{10}$, or CH_2NHR_{11} .

34. The method of claim 33 further comprising the step of reacting the compound of formula (XII) with $R_3\text{-MgBr}$, where R_3 is $(C_1\text{-}C_4)\text{alkyl}$, $(C_1\text{-}C_4)\text{alkenyl}$ or $(C_1\text{-}C_4)\text{alkynyl}$; and $((C_1\text{-}C_4)\text{alkyl})_3\text{SiCl}$ to synthesize a compound of formula (XIII):

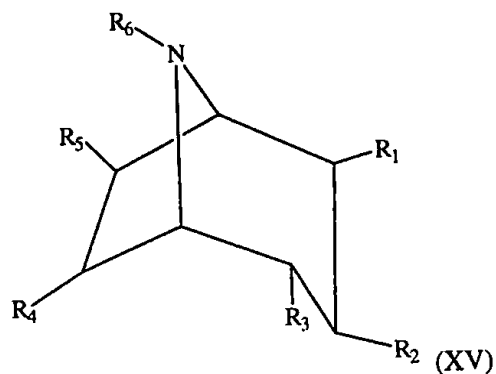


35. The method of claim 34 further comprising the steps of reducing the keto group in the compound of formula (XIII) to yield a compound of formula (XIV):



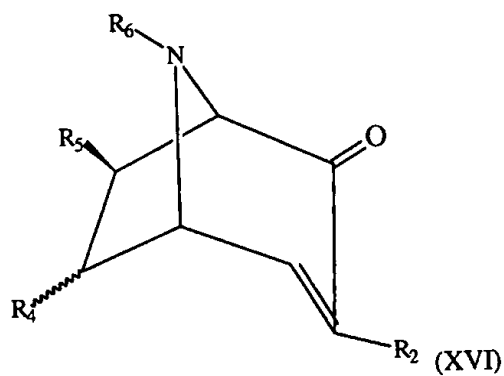
and reacting the compound of formula (XIV) with an anhydride of the formula $\text{CH}_3\text{C(O)O-R}_7$ where R_7 is $(C_1\text{-}C_4)\text{alkylC(O)-}$ or $(C_5\text{-}C_7)\text{arylC(O)-}$ to yield a compound of formula (XV):

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wherein R_1 is OR_7

36. A method of synthesizing a compound of formula (XVI):



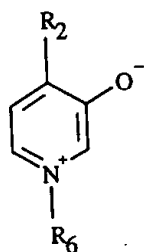
wherein

R_2 is phenyl or benzyl, optionally substituted with halo, CF_3 , (C_1-C_4) alkoxy, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl, amino, nitro or (C_5-C_7) aryl;

R_4 and R_5 are H or SO_2Ph , where one of R_4 or R_5 is H, and the other is SO_2Ph ; and

R_6 is H, (C_1-C_4) alkyl, (C_1-C_4) alkenyl, (C_1-C_4) alkynyl or benzyl;

comprising the steps of reacting a compound of formula (IV):



(IV)

with $\text{CH}_2=\text{CH}-\text{SO}_2\text{Ph}$.

37. A compound of claim 1 or 29 for use in medical therapy.
38. The use of a compound of claim 1 or 29 for the manufacture of a medicament useful to induce analgesia or vasoconstriction in a mammal, or to treat cocaine abuse, depression, obesity, or Parkinson's disease in a mammal.
39. The invention also provides a radiolabeled compound comprising a radionuclide bound to a compound of formula I for use in medical imaging.
40. The use of a radiolabeled compound comprising a radionuclide bound to a compound of formula I, for the manufacture of a medicament useful for medical imaging.

Figure 1

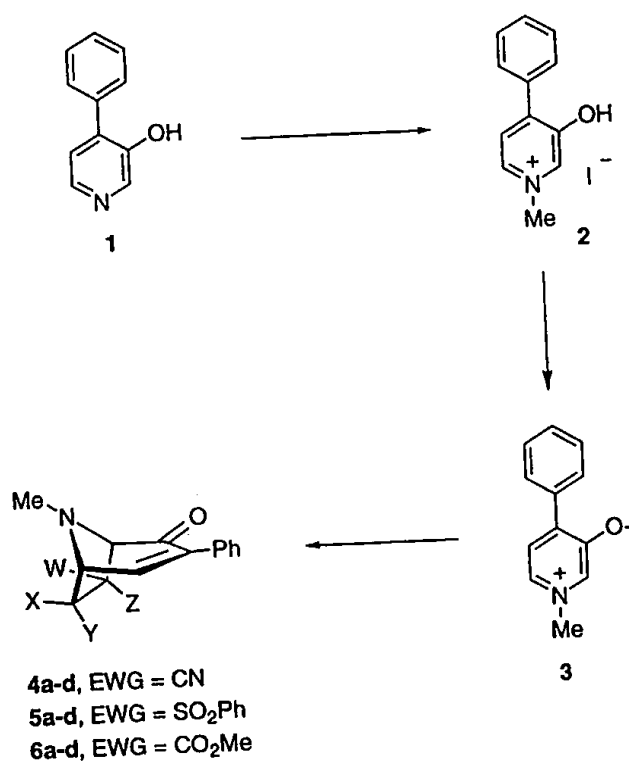


Figure 2

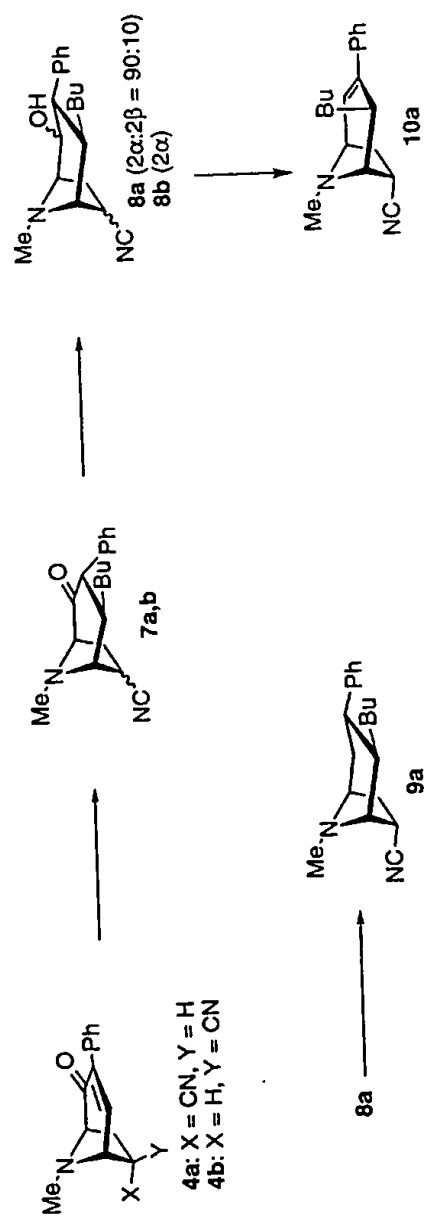
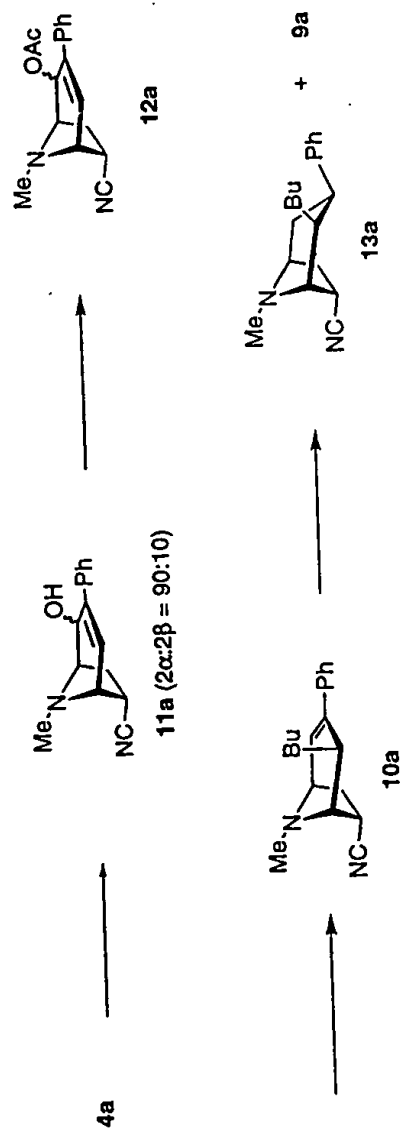


Figure 3



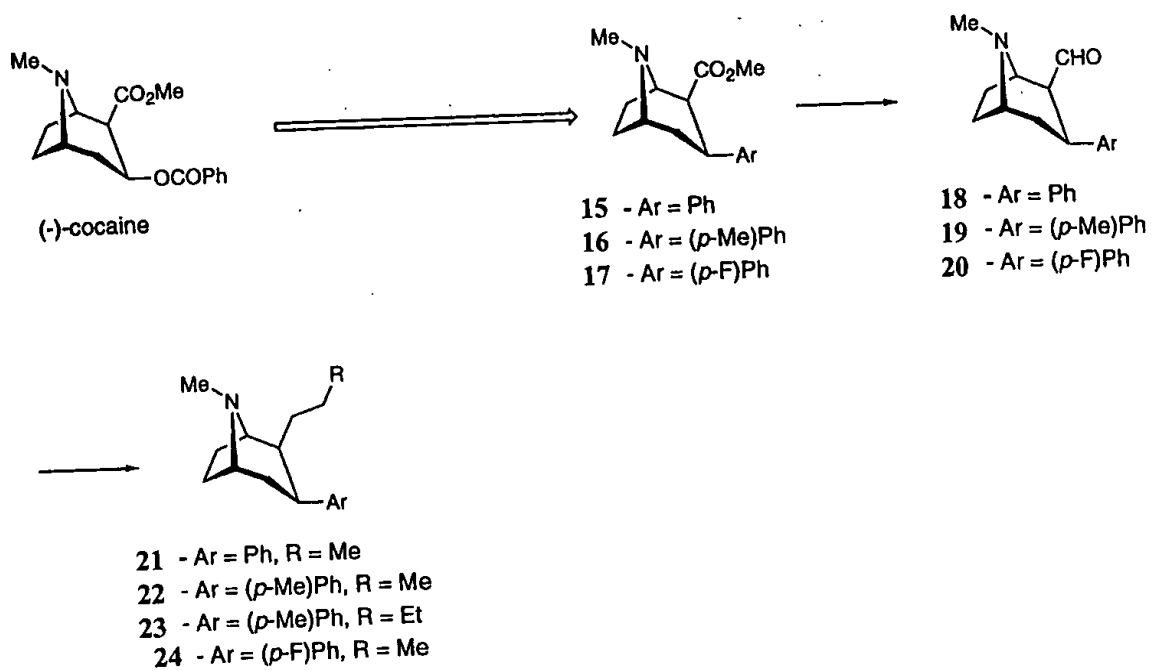


FIG. 4

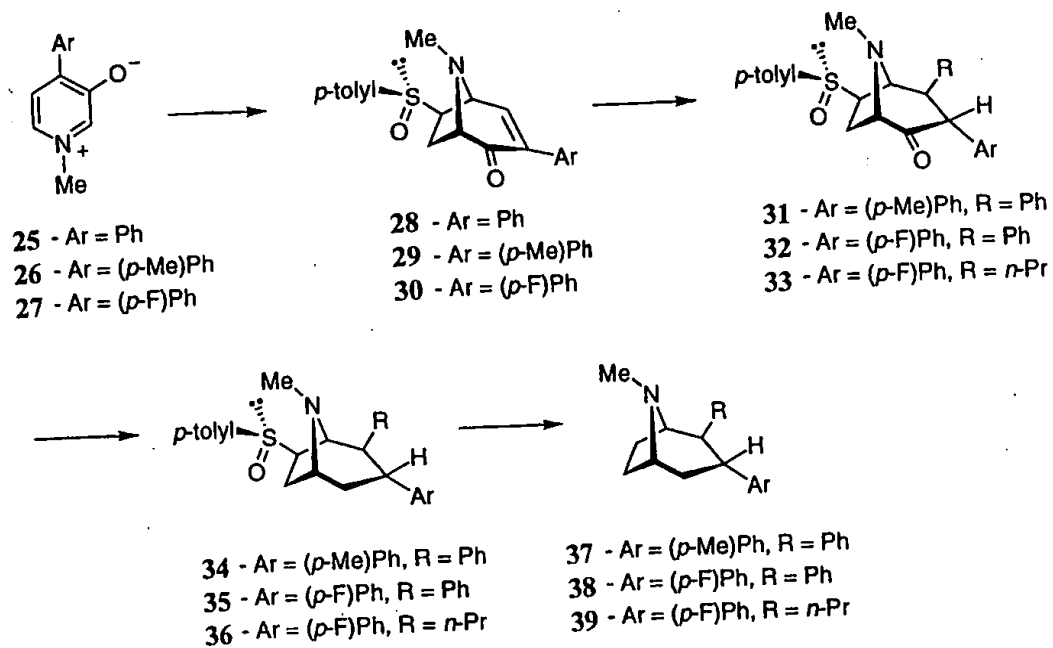


FIG. 5

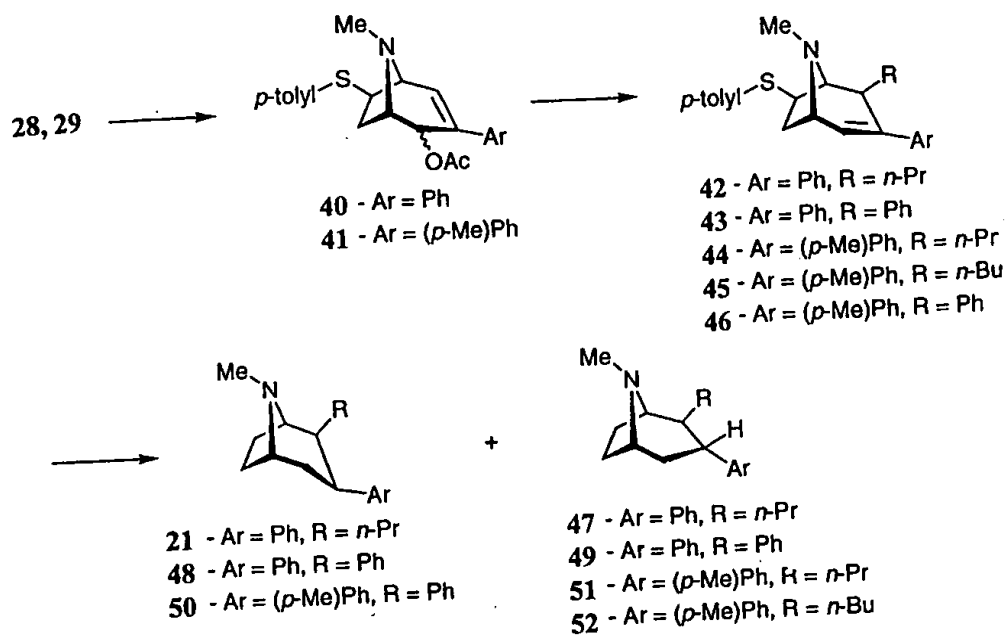


FIG. 6

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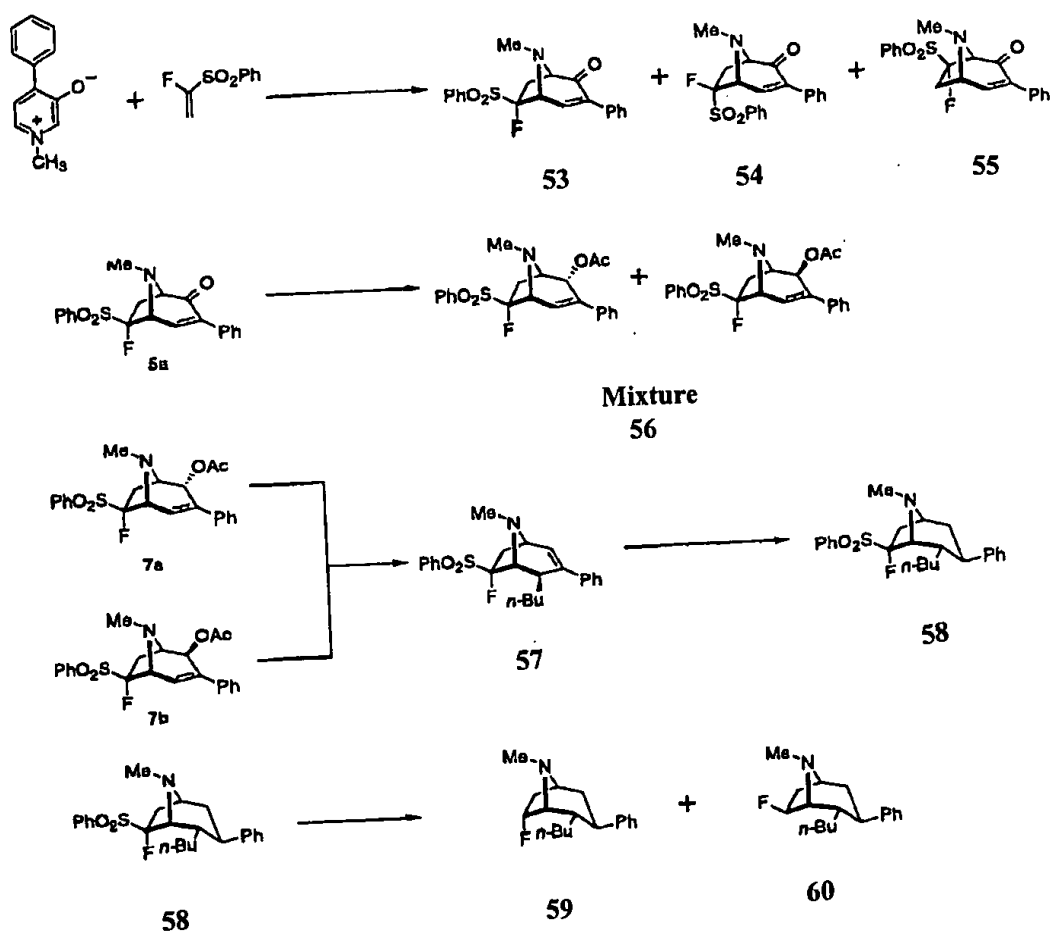
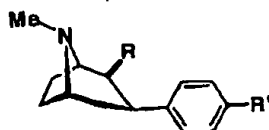


FIG. 7



compd	R	R'	isomer	Mazindol Binding		[³ H]DA Uptake		[³ H]5-HT Uptake		ratio 5-HT/DA
				IC ₅₀ ^a	KI ^a	IC ₅₀ ^a	KI ^a	IC ₅₀ ^a	KI ^a	
	cocaine				280		320			
15	CO ₂ Me	H	2β, 3β	163.1	89.4	57.9	53.7	203.9	185.6	3.4
16	CO ₂ Me	Me	2β, 3β	10.5	5.8	7.5	6.92	25.5	23.2	3.36
21	n-Pr	H	2β, 3β	23.1	12.2	7.5	6.89	95.4	86.8	12.6
47	n-Pr	H	2β, 3α	141.4	74.9	32.6	30.2	427.6	389.4	12.9
22	n-Pr	Me	2β, 3β	2.97	1.6	1.19	1.10	11.3	10.3	9.35
51	n-Pr	Me	2β, 3α	18.2	8.9	12.7	11.8	54.8	50.1	4.25
23	n-Bu	Me	2β, 3β	3.43	1.82	1.42	1.31	16.5	15.1	11.5
52	n-Bu	Me	2β, 3α	21.6	11.4	10.9	10.1	55.8	50.9	5.07
48	Ph	H	2β, 3β	96.5	49.9	31.1	28.9	1200.0	1100	38.1
49	Ph	H	2β, 3α	26.6	13.8	12.6	11.7	822.5	752.7	69.3
50	Ph	Me	2β, 3β	4.98	2.58	3.09	2.87	80.8	73.77	25.7
37	Ph	Me	2β, 3α	5.55	2.87	4.48	4.16	314.1	286.9	64.6

^aData are expressed in nM

FIG. 8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/21706

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07D 451/02; A61K 31/46

US CL :546/124; 514/304

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/124, 127, 132; 514/304

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE, APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KOZIKOWSKI. A.P. et al. Chemistry and biology of the 2-alkyl-3-phenyl analogues of cocaine. J. Med. Chem. 1995, Volume 38, pages 3086-3093, especially table 2 on page 3089.	1,3,7,14,16, 22-32, 37-40
X,P	KOZIKOWSKI, A.P. et al. Dipolar cycloaddition route to diverse analogues of cocaine. J. Org. Chem. 1997, Volume 62, pages 503-509, especially compounds 11a, 11b, 12a on page 504 and compounds on page 506.	1-6, 8-11, 13, 14, 16, 22-32, 37-40
A	US 5,444,070 A (MOLDT et al) 22 August 1995, claims 1-9.	1-16, 22-32, 37-40

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

B earlier document published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

A

document member of the same patent family

Date of the actual completion of the international search

23 MARCH 1998

Date of mailing of the international search report

06 APR 1998

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
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Washington, D.C. 20231

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Authorized officer

CHANN AULAKH

Telephone No. (703) 305-1215

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/21706

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-16, 22-32 and 37-40

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/21706

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

I. Claims 1-16, 22-32 and 37-40 are directed to Compounds of formula (I), pharmaceutical composition and method of treatment using compounds of formula (I), classifiable in class 514, subclass 304.

II. Claims 17-20 are directed to a method of synthesizing compounds of formula (III), classifiable in class 546, subclass 127+.

III. Claim 21 is directed to a method of synthesizing compounds of formula (X), classifiable in class 546, subclass 124+.

IV. Claims 33-36 are directed to a method of synthesizing compounds of formula (XII), classifiable in class 546, subclass 132+.

The inventions listed as Groups I through IV do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:
The inventions I through IV as defined above are combinations of different categories of claims since the processes of inventions II, III and IV are different processes and furthermore, are not directed to preparing compounds of invention I, see PCT Administrative Instructions Annex B, Part I (e).